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The implementation of an individualised continuous positive airway pressure programme in preparation of the intubated adult patient for extubation

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CHAPTER 1

1. INTRODUCTION

1.1 BACKGROUND

The primary objectives of mechanical ventilation (MV) are to decrease the work of breathing, reverse life-threatening hypoxaemia and acute progressive respiratory acidosis, improve oxygenation and prevent lung injury (Tobin, Brochard and Rossi 2002). A prospective, international study of 1638 patients in eight countries found that some of the indications for MV included acute respiratory failure (66%), coma (15 %), acute exacerbation of chronic obstructive pulmonary disease (COPD) (13%) and neuromuscular disorders (5%) (Esteban, Ferguson, Meade, Frutos-Vivar and Apezteguia 2000). They reported that 39% of patients in the intensive care unit (ICU) are mechanically ventilated for an average duration of seven days. According to the above mentioned authors common disorders that lead to acute respiratory failure include acute respiratory distress syndrome, heart failure, pneumonia, sepsis, complications of surgery and trauma.

Mechanical ventilation, although often life saving, can cause various life-threatening complications such as ventilator-associated pneumonia (VAP) and ventilator-induced diaphragmatic dysfunction. These complications can increase morbidity and mortality up to three fold (Ambrosino 2005). It is therefore important to discontinue ventilator support as soon as possible. Ventilator-induced diaphragmatic dysfunction and atrophy of the diaphragm occur after as little as 18-69 hours of diaphragmatic inactivity associated with MV (Callaghan 2008). Data have revealed a 50% or more reduction in the cross-sectional areas of human diaphragmatic fibres (Tobin, Laghi and Jubran 2010; Ambrosino 2005; MacIntyre 2005). The degree of dysfunction of the respiratory muscles is directly related to the relative contribution of the ventilator and patient. Inactivity or low levels of activity of the respiratory muscles, as seen in patients that require high levels of ventilatory assistance, is likely to lead to a higher degree of respiratory muscle inactivity (Callahan 2008; Levine, Nguyen, Taylor, Friscia, Budak, Rothenberg, Zhu, Sachdeva, Sonnad, Lasier, Rubinstein, Powers, and Shager 2008; Sieck and Mantilla 2008; Vassilakopoulos and Petrof 2004; Sassoon 2002; Shanely, Zergeoglu, Lennon, Sugiura, Yimlamai, Enns, Belcastro and Powers 2002; Yang, Luo, Bourdon, Lin, Gottfried and Petrof 2002). An imbalance between the load on the respiratory system and respiratory muscle strength and endurance is a major contributory factor to weaning failure (Boles, Bion, Connors, Herridge, March, Melot, Pearl, Silverman, Stanchina, Vieillard-Baron and Welte 2007; Frutos-Vivar, Ferguson, Esteban, Epstein, Arabi, Apezteguia, Gonzalez, Hill, Nava, E'empaire and Anzueto 2006; Nava, Piaggi, De Matta and Cavlucci 2002; Zakynthino,

Vassilakopoulos and Roussos 1995). Continuing problems with weaning may be the result of weaning strategies that provide neither sufficient muscle work nor sufficient rest. This leads to fatigue of the respiratory muscles and diaphragm, which can take up to 24 hours to recover (Meade, Guyatt, Cook, Griffith, Sinuff, Kergl, Mancebo, Esteban and Epstein 2000; Laghi, D'alfonso and Tobin 1995). One of the main causes for failed weaning is ventilator-induced diaphragmatic dysfunction (Petrof, Jaber and Matecki 2010; Ambrosino 2005; MacIntyre 2005). During the time that the patient recovers from ventilator-induced diaphragmatic dysfunction, additional mechanical ventilatory support would be required, with the possibility of added ventilator induced complications, increased mortality rate and medical cost (Ambrosino, 2005; Meade et al 2000).

Weaning from MV normally consists of three stages (Meade et al 2000). Different modes of ventilation can be used according to the individual needs and symptoms of the patient. Stage one is the weaning stage when there is a stepwise reduction in ventilatory support. More than 40% of the total time that the patient receives MV is spent in the weaning stage (Clarkson and Hubal 2002). During this stage the patient is still critically ill but relatively stable and ventilatory support is gradually weaned by progressively reducing the level of assisted breathing support provided (Meade et al 2000). This can be done by gradually decreasing the a) pressure support, b) ventilator rate, c) fraction of inspired oxygen (FiO_2), d) trigger flow and/or e) positive end expiratory pressure (PEEP) and redirecting the work to the patient (Newmarch 2006). Stage two is the spontaneous breathing trial (SBT) stage. During this stage a SBT is performed to assess a patient's ability to breathe independently (Wratney and Cheifetz 2006). Stage three is the extubation stage, when the patient is liberated from the ventilator and extubated (Meade et al 2000). For the purpose of this study stage one was divided into 2 stages. This was done to differentiate the time that the patients spent on full MV and time spent on stepwise weaning. Stage 1 (maximum MV support stage) starts when the critical, unstable patient is intubated and maximum ventilatory support, according to the needs and symptoms of the patient, is instituted. Stage 1 can be influenced by various factors, which is not in the scope of this study and hence will not be discussed further. Stage 1 normally lasts for only a few hours before the ventilatory support is gradually weaned, which is the start of stage 2 (weaning stage). Once the ventilatory support is weaned to provide minimal assistance and the patient does not show any signs of distress, episodes of spontaneous breathing are introduced, which marks the beginning of stage 3 (spontaneous breathing stage). Spontaneous breathing can be achieved by putting the patient on a T-piece with oxygen flow-by (without the support of airway pressure) or a T-piece with oxygen flow-by with a PEEP valve attached to the end of the oxygen tubing or on continuous positive airway pressure (CPAP)

mode on the ventilator, alternated with periods of assisted MV. Continuous positive airway pressure provides a set continuous amount of pressure to the airways whereas pressure support ventilation only provides support on inspiration and therefore cannot compensate for the non-linear, flow dependant resistant workload of the endotracheal tube (Petrof et al 2010). The pressure support and PEEP levels during CPAP mode on the ventilator can be adjusted to ensure that the patient remains comfortable while breathing on his own.

Spontaneous breathing during MV is usually almost immediately followed by an increase in respiratory rate and a fall in tidal volume – this is defined as rapid shallow breathing due to an increase in work rate of breathing (WOB). This elevated workload is imposed on a weakened respiratory muscle pump (Heunks and Van der Hoeven 2010). The WOB of the patient may increase considerably, reaching more than four times the normal value at the end of the spontaneous breathing period due to fatigue of the diaphragm and respiratory muscles as well as the resistance of airflow through the endotracheal tube (Tobin, Brochard and Rossi 2002). Imposed WOB comes from the extra forces required by the patient to overcome airway resistance and the elastic forces of the lungs and chest wall (Petrof et al 2010; Cohen, Shapiro, Grozovski, Lev, Fisher and Singer 2006). Therefore this stage needs to be well managed to prevent diaphragmatic fatigue and subsequent respiratory distress. Once the patient can sustain spontaneous breathing periods with minimal ventilatory support, extubation will be done (stage 4). Extubation from MV is done by either extubation or by continuous tracheal oxygen mask and/or T-piece without any mechanical ventilatory support (Stawicki 2007; Wratney and Cheifetz 2006; Hough 2001).

Up to 20% of patients may need to be re-intubated due to respiratory distress (Stawicki 2007; Frutos-Vivar et al 2006; MacIntyre 2005, MacIntyre 2002; Tobin et al 2002). The mortality rate of patients who are re-intubated is six times higher than those who do not require re-intubation (Esteban, Inmaculada, Gordo, Fernandez, Solsona, Vallverdu, Macias, Alleque, Demetrio, Carriedo, Leon, De La Cal, Taboada, Gonzalez, De Velasco, Carrizosa, Tomas, Suarez and Goldwasser 1997); hence extubation should only be performed if the patient has adequate respiratory muscle strength and endurance to sustain the effort of spontaneous breathing. Assessing the patient's respiratory muscle strength before spontaneous breathing episodes and the timing of extubation is therefore recommended in order to prevent respiratory muscle fatigue and to prevent or decrease the incidence of extubation failure.

The severe shortage of specially-trained intensivist physicians who can lead the ICU team is an international phenomenon, but a multidisciplinary approach to patient management in the

absence of trained intensivists can reduce mortality by a significant 12% (Kahn, Fleisher, Kim, Barnato and Angus 2010). There is a serious shortage of fulltime specially-trained intensivist physicians in the private health sector in South Africa, which is more prevalent in the rural areas (Scribante and Bangwanjee 2007).

The European Society of Critical Care Medicine advocates that the optimal method for care delivery in the ICU is the team model approach and that a dedicated respiratory therapist should form part of the ICU team (Gosselink, Bott, Johnson, Dean, Nava, Norrenberg, Schonhofer, Stiller, Van de Leur and Vincent 2008; Durbin 2006). There are no respiratory therapists in South Africa and therefore physiotherapists are responsible for the management of the ICU patient's respiratory rehabilitation, bronchial clearance and physical rehabilitation, but do not generally take an active part in the weaning strategies of patients on MV (Van Aswegen and Potterton, 2005). As the experts in exercise physiology in the professional ICU management team, physiotherapists should take an active role in the weaning process and respiratory rehabilitation of patients receiving MV (Dean 2006).

The health status of the majority of patients in private rural ICU's in South Africa as well as unique staffing burdens facing these units place an additional challenge on the management of these patients. According to figures from the World Factbook 2009 and from the 2006 revision of the United Nations World Population Prospects report (2005 -2010), South Africa has one of the highest rates of patients living with HIV and AIDS in the world. Adult rates range from 25.4% to 38.8% (Myezwa, Stewart, Mbambo and Nesar 2007). The life expectancy of the world at birth was 67.2 years for 2005 -2010 but only 49.3 years for South Africa (CIA World Factbook, 2011). This has been taken into consideration during the inclusion criteria, especially with regards to the age of the sample population, in the current study.

There is a critical shortage of specialised trained professional ICU nurses in South Africa (De Beer, Brysiewicz and Bhengu 2011; Colyn 2008; Scribante, Schmollgruber and Nel 2004). Between 25 to 50% of nurses in ICU's in South Africa are qualified ICU nurses. The rest of the nursing staff compliment is made up by registered general nurses whose training was mainly, focused on primary health care. Due to the shortage of nursing staff in private ICU's in South Africa, agency nurses are utilised. These are usually registered nurses who are employed in the public government hospitals who take on added shifts in the private sector to supplement their income. According to Scribante, Schmollgruber and Nel 2004 (2004), 21 % of nurses working in ICU's in South Africa are general enrolled nurses who lack the experience and training for this highly technical medical environment. The general open rural private ICU in

South Africa also does not have the privilege of a full time trained intensivist to manage the patients in these units (Scribante and Bangwanjee 2007). The medical management and mechanical ventilatory management of these patients are usually undertaken by the attending physicians, surgeons or anaesthetists who apart from managing the ICU patients, still have to fulfil their normal hospital duties and outpatient practice. The same is true for the physiotherapists and other health care practitioners such as dieticians who work in these settings. All of these factors may contribute to a lack of evidence based management strategies for weaning of critically ill patients (Kahn et al 2010).

1.2 PROBLEM STATEMENT AND JUSTIFICATION FOR RESEARCH

Patients that are not adequately managed during the weaning and spontaneous breathing stages of MV are at risk of developing ventilator-induced diaphragmatic dysfunction and respiratory distress. This may lead to prolonged MV and a delay in the weaning process and hence the risk of exposure to all the complications of MV and ICU length of stay namely VAP, increased morbidity and mortality.

A systematic well planned approach to the weaning process for mechanically ventilated patients has been demonstrated by various authors to yield the best results and halve the rate of complications mentioned above (Esteban, Ferguson, Meade, Frutos-Vivar and Apezteguia 2007; Grap, Stickland, Tormek, Lubin, Keane, Dalby, Townes and Sessler 2003; Ely, Meade, Haponik, Kollef, Cook, Guyatt and Stoller 2001; Vitacca, Vianello, Colombo, Clini, Porta, Bianchi, Arcaro, Vitale, Guffanti, Lo Coso and Ambrosino 2001). Contrary to the above evidence, in the clinical setting many patients on MV are still managed without a set of predetermined scientific screening procedures for weaning readiness or a systematic weaning protocol for termination of MV. Weaning is often done according to the preference, subjective evaluation and experience of the attending physicians or nursing staff and not according to the patient's individual capability. Often no objective measurements are taken to assess the patient's readiness for weaning or extubation. Many physicians disregard published evidence-based guidelines on these procedures and do it "their way" instead (Epstein 2009; Begany 2002). Guidelines and protocols should enhance, not replace, clinical judgement and should be used to allow appropriate decision making and an improvement in clinical outcomes (Esteban et al 2007; Ely et al 2001). The purpose of this study is to assess the value of an individualised CPAP program during the spontaneous breathing stage of adult patients that are mechanically ventilated in preparation for extubation.

1.3 SIGNIFICANCE OF RESEARCH

Physiotherapists form an integral part of the multidisciplinary team in almost all ICUs' in South Africa and internationally. A large portion of the four year undergraduate training programmes for physiotherapists in South Africa involves training and clinical reasoning in human anatomy, physiology, pathology and exercise science. However physiotherapists do not, always apply their expert knowledge of exercise physiology, clinical reasoning and evaluation skills to the weaning strategies of patients who are mechanically ventilated (Gosselink et al 2008; Dean 2006)

Patients that are mechanically ventilated generally present with decreased skeletal muscle power that might be due to a) the catabolism of critical illness, b) decreased energy intake due to poor absorption of nasogastric feed, c) effects of certain medication administered in ICU such as paralysing agents, certain antibiotics and corticosteroids and d) recumbency (Bittner, Martin, Edward, Frontera and Eikermann 2009; Gosselink et al 2008). There is a growing body of evidence that suggests that early mobilisation of patients that are mechanically ventilated in ICU does have beneficial effects on patient management and rehabilitation (Choi, Tasota and Hoffman 2008; Gosselink et al 2008; De Jonghe, Bastuji-Garin, Durand, Malissin, Rodriques, Cerf, Outin and Sharshar 2007). Early rehabilitation and mobilisation of patients that are mechanically ventilated should therefore be a part of the multidisciplinary team approach to the management of all these patients.

The role of the physiotherapist in the management of adult patients who are ventilated in South Africa is generally limited to the management of bronchial hygiene, positioning and mobilisation (Van Aswegen and Potterton 2005). As mentioned previously physiotherapists in South African ICUs are rarely involved with weaning of patients from MV (Van Aswegen and Potterton 2005). The researcher decided to apply principles similar to rehabilitation to the spontaneous breathing stage (stage 3) of patients who are mechanically ventilated to investigate its effects on the preparation of such patients for extubation. Involving the physiotherapist in the weaning process and extubation of patients may expand the role of the physiotherapist in the ICU's in South Africa. By taking an active role in the screening and weaning process of ventilated patients, physiotherapists could contribute towards improved patient care and outcomes such as decreased MV days and by implication decreased cost of health care.

The McMaster University Evidence-Based Practice Centre together with the Agency for Health Care Policy and Research (AHCPR) (MacIntyre, Cook, Epstein, Carson, Scheinhorn, Christopher and Muldoon 2005) conducted a comprehensive literature review regarding the

development and implementation of weaning protocols. The use of non-physician health care providers (respiratory-care practitioners, physiotherapists and nurses) in the ICU to ensure successful weaning of patients from MV was one of the strongest recommendations reported from this study. Positive weaning and extubation outcomes were also achieved in multi-professional and intra-professional collaboration in various other studies on weaning (Garrubba, Hof and Younes 2009; Lingard, Espin, Evans and Hawryluck 2004; Chan, Fisher, Stewart, Hallet, Hynes-gay, Lapinsky, Mac Donald and Mehta 2001). These findings have clinical relevance to all aspects of critical care medicine and nursing. This research project was a collaborative process between the physiotherapy and nursing departments of the Faculty of Health Sciences of the University of the Witwatersrand.

1.4 RESEARCH QUESTION

Could the implementation of an individualised graded CPAP program, during the spontaneous breathing stage of a weaning protocol, improve the preparation of a patient for extubation and therefore improve the outcomes of weaning and extubation, in adult ventilated patients?

1.5 RESEARCH AIMS

The aim of this study was to develop, implement and test the outcomes of an individualised graded CPAP protocol implemented during the spontaneous breathing stage of weaning, utilizing the principles of rehabilitation; stepwise daily progression according to the individual's needs and progression with adequate rest and recovery periods, for adult subjects who were mechanically ventilated.

1.6 RESEARCH OBJECTIVES

1.6.1 General Objectives

- To establish whether the use of an individualised graded CPAP protocol during the spontaneous breathing stage of a weaning protocol is more effective in improving weaning outcomes for subjects on MV than a standard weaning protocol.

1.6.2 Specific Objectives

- To determine the availability of a set of non-invasive, easy-to-use and readily available clinical screening tools to be used as indicators to evaluate the strength and endurance of the respiratory muscles of adult subjects who were mechanically ventilated.
- To determine the availability and clinical appropriateness of a test that could predict the duration that a subject could sustain spontaneous breathing episodes before task failure. Task failure is an event defined by the inability to continue performing the required task, in this context, spontaneous breathing.

- To develop and implement a CPAP protocol, utilising basic muscle rehabilitation principles, which could be individualised for each adult subject who was mechanically ventilated. These principles will be discussed in detail in the literature review (Chapter 2) of this document.
- To measure the effectiveness of the individualised CPAP protocol in the 3de stage of MV (spontaneous breathing stage) on the outcomes of adult subjects who were mechanically ventilated. [Outcomes: time spent in stage 2 and 3 of MV, failure rate of the subject's ability to sustain spontaneous breathing in stage 3 of MV, successful extubation, reasons for extubation failure, reasons for stage 3 of MV failure, the mortality rate during stages 3 to 4 of MV, total days on MV and the overall length of ICU stay].

1.7 TYPE OF STUDY

An experimental, prospective, non-randomised, sequential study of two groups of subjects was performed. Group one was the control group and group two the intervention group. This study design was chosen due to the following practical reasons in the test setting:

- The test setting was an 11 bed, general open adult ICU in a private hospital in a rural town in South Africa. The test setting did not have a full time intensivist; the management of the patients on MV was done by the attending physician, surgeon or anaesthetist, who apart from managing the ICU patients, ran a private outpatient practice as well as attended to normal in-hospital patients. According to the unit manager about 20 percent of the permanent nursing staff were trained ICU nurses, the rest were generally trained registered nurses. The unit made use of approximately 50 percent of agency staff especially during weekends.
- The staff-subject ratio of 1:2 made it potentially difficult to have a non-intervention control group as one staff member may have had to nurse two subjects during the same shift, each in a different group. Such a situation could have led to contamination of data as well as spill over of the intervention to the control group. Due to the close working environment of all staff involved in this study, it would have been impractical to do a blinded randomised controlled study.
- The decision to first capture the data of the control group and then do the intervention was done to prevent the possible contamination of control group's data due to the learning effect that the staff could have had if the sequence was reversed.

1.8 SUMMARY

Mechanical ventilation has the potential to cause life-threatening complications such as VAP and ventilator-induced diaphragmatic dysfunction, with the associated risk of increased morbidity and mortality. It is therefore important to discontinue MV as soon as possible. Weaning strategies that provide insufficient respiratory muscle work, overuse or insufficient respiratory muscle rest may lead to respiratory muscle fatigue and consequently failed weaning and extubation. The main aim of this study was to test the implementation of an individualised CPAP protocol on the outcomes of weaning and extubation in a group of adult subjects who were mechanically ventilated.

Chapter 2 consists of a detailed discussion of the literature on MV, weaning strategies, respiratory muscle physiology and general muscle rehabilitation principles.

CHAPTER 2

2. LITERATURE REVIEW

This literature review aims to evaluate evidence found in the medical literature on the indications for MV, weaning strategies, respiratory muscle physiology and muscle rehabilitation principles related to this research study.

2.1 INDICATIONS FOR MECHANICAL VENTILATION IN ADULT PATIENTS

Intensive care units are the structures in which MV is applied and MV is practiced universally in ICUs around the world (Branson 2002). It has revolutionised the management of critically ill patients in the last five decades (Prakash, Krishna and Bhatia 2006). It is indicated in any medical or surgical condition where the patient's spontaneous ventilation is inadequate to sustain life and therefore MV is used in the management of approximately 90% of critically ill adults in ICU's (McLean, Jensen, Schroeder, Gibney and Skjodt 2006). Mechanical ventilation is also indicated as prophylaxis for threatening collapse of other physiological functions and as a measure to control ventilation in critically ill patients (Byrd, Quillen, Kosseifi and Roy 2010). Many factors will affect the decision to initiate MV. Patients should have a correctable underlying problem that can be resolved with the support given from MV as no mode of MV can cure a disease. Common indications for MV include respiratory failure with associated bradypnea or tachypnea, acute lung injury, acute respiratory distress syndrome (ARDS), trauma, overdose, post-surgery complications and cardiac complications (McLean et al 2006). Although the main aim of MV is to prevent death, the complications associated with prolonged MV can be life threatening.

2.2 COMPLICATIONS OF MECHANICAL VENTILATION

Prolonged MV, defined as MV for more than 48 hours, can expose patients to unnecessary risks and complications, such as VAP, airway trauma, complications of intubation, ventilator-induced lung injury such as baro- and volutrauma as well as ventilator-induced diaphragmatic dysfunction (Cook, Walters and Cook 1998). A survey done by Prakash, Krishna and Bhatia (2006) on 100 patients that presented with respiratory failure concluded that 55% of patients on MV in the ICU may develop the above mentioned complications. These complications of MV can occur due to many factors and at any stage of ventilation. Premature extubation can be equally problematic and carries its own set of risks, including difficulty to re-establish an airway, eight-fold higher odds ratio for VAP, compromised gas exchange and a six- to 12- fold mortality risk (Stawicki 2007). The mortality rate of patients on prolonged MV in the United States, in a multiple centre survey, was 35% (Zilerberg, Luippola, Sulsky and Short 2008; Ambrosino 2005).

Zwillich, David, Creaqh, Sutton, Schatz and Petty (1974) classified the complications of MV into three categories. The first category was attributed to airway accidents such as intubation injuries, tube malfunction and accidental extubation. The overall incidence of airway accidents can reportedly be as high as 7% of all MV patients (Esteban et al 2002). The second category comprised complications due to the operation of the ventilator, which included machine failure (1.7%) and alarm failure (3.7%). According to Zwillich et al (1974) the third and last category included medical complications which occur during assisted MV such as alveolar hypoventilation (9.9%), hyperventilation (11%), massive gastric distension (1.4%), sepsis (9.7%), acute renal failure (18.7%), barotraumas (3%), ARDS (22.1%), shock (22.1%), coagulopathy (10.6%), respiratory acidosis (5.6%), metabolic acidosis (6.7%) and VAP (30%), Esteban et al (2002) supported these findings. Some patients with critical illness do wean quickly from MV and can be extubated without any complications. In approximately 10 to 20% of patients ventilated for longer than 21 days the weaning and extubation process can be extremely difficult and lengthy, due to the abovementioned complications (Stawicki, 2007). Ventilator-acquired pneumonia is a life-threatening complication with mortality rates of 33%-50% and is defined as a new parenchymal lung infection that occurs after initiation of mechanical ventilation (Byrd et al 2010). Ventilator-acquired pneumonia is the most common and lethal form of hospital-acquired pneumonia or noso- comial pneumonia (Byrd et al 2010). The risk of VAP is at its highest immediately after intubation and is estimated to occur at a rate of 3% per day for the first five days, 2% per day for the next five days and 1% thereafter (Byrd et al 2010).

Smoking impairs muscle protein synthesis and increases the expression of myostatin in muscle giving rise to impaired muscle maintenance (Peterson, Magkos, Atherton, Selby, Smith, Rennie, Pedersen and Mittendorfer 2007). Patients living with HIV reported co-morbidities such as peripheral neuropathies (46%), tuberculosis (TB) (37%) and pneumonia (10%-29%) (Maharaj and Rangiah 2010; Myezwa et al 2007). Immune mediators, such as interleukin-1 and interleukin -2 (present in patients living with HIV), can affect body composition through modulation of appetite and food intake and directly effects skeletal muscle (Thomas 2007). It can therefore be assumed that smokers and patients living with HIV who are on prolonged mechanical ventilation might be more at risk for developing complications associated with MV.

Mechanical ventilation can have detrimental effects on respiratory muscle fibres (Caruso, Carniele, Kagohara, Anciaes, Segarra and Deheinzelin 2008; DeBoisblance, Goldman, Mayberry, Brand, Panburn, Soifer and Mullins 2000) as a direct result of the imbalance

between the load on the respiratory system, the quantity and quality of ventilator support and the capacity of the respiratory muscles (Nava et al 2002).

2.3 THE EFFECT OF MECHANICAL VENTILATION ON RESPIRATORY MUSCLES

Due to the effects that MV and weaning strategies may have on skeletal muscles, a short explanation of the basic physiology and classification of skeletal muscle fibres, and in particular respiratory muscles fibres, will be provided.

2.3.1 Classification of Skeletal Muscle Fibre Types

There are two principle types of skeletal muscle cells namely:

a) Type I, slow twitch (ST) or red fibres; and

b) Type II, fast twitch (FT) or white fibres.

The two types of muscle cells are mixed throughout the different muscles of the body with the concentration of each depending on the primary function of each muscle, whether it is endurance, power or both. The two types can be differentiated on the basis of their colour, the speed at which they contract and the quantity of mitochondria that they contain (McArdle, Katch and Katch 1996; Guyton 1979).

Type I fibres are red in colour due to a high concentration of mitochondria with a high protein content, myoglobin. The function of myoglobin is to store oxygen in the muscles and to transfer the oxygen carried in blood to the mitochondria. Type II fibres; however, are white due to low myoglobin content.

Type I fibres contract and relax slower than type II fibres. The strength of the adenosine triphosphate (ATP)-specific enzyme, myosin adenosine triphosphate (ATPase), which sits in the myosin head and to which ATP binds, determines the speed of a muscle fibre contraction. Slow contracting red fibres have less myosin ATPase activity than fast contracting white fibres (McArdle, Katch and Katch 1996). Type I, ST fibres have a high concentration of mitochondria and therefore an increased capacity to produce ATP by oxygen-dependant metabolism in the mitochondria as is found in muscles than mainly perform endurance activities. Type II, FT fibres are found mainly in muscles that perform power activities due to the decreased amount of mitochondria and decreased capacity to produce ATP (McArdle, Katch and Katch 1996; Noakes 1990).

2.3.2 Physiological Properties of Respiratory Muscles

The primary respiratory muscles in humans are the diaphragm and the intercostal muscles. These have, as do all skeletal muscles, type I Slow Twitch (ST) and type II Fast Twitch (FT)

individual muscle fibres. The diaphragm in healthy subjects older than two years has 54.9% type I ST and 46.1% type II fibres FT (Polla, D'Antona, Bottinelli and Reggiani 2004); therefore the diaphragm is better equipped to endure long periods of activity and less well equipped for strenuous hard work. Under normal conditions the diaphragm has a large reserve capacity due to the fact that only a small fraction of the diaphragm's total force-generating capacity is used to sustain spontaneous breathing. The diaphragm is active 24 hours a day, compared to other muscles in the body which are active only a small percentage of the day (Keens, Bryan, Levison and Lanuzzo 1978). To achieve this level of activity, the diaphragm fibres used for breathing must be resistant to fatigue and need to have a high endurance capacity; therefore if the diaphragm has been fatigued, spontaneous breathing cannot be sustained indefinitely. This is of clinical significance in the management and weaning strategies of patients on MV.

A key component of acquired weakness syndrome in patients on MV is the development of respiratory muscle weakness, which in turn leads to prolonged ventilation, difficulty with weaning patients from the ventilator and recurrence of respiratory failure after extubation (Callahan 2008). In a narrative review on ventilator–induced respiratory muscle weakness Tobin (2011) stated that research on ventilator induced respiratory muscle injury is in its infancy and is an exciting area to follow. Petrof et al (2010) also stated that there has recently been a great expansion in the knowledge of how MV adversely affects diaphragmatic structures and function.

Five different effects of MV on respiratory muscles (collectively known as ventilatory induced diaphragmatic dysfunction) have been described in the literature and will be discussed below.

2.3.3 **Muscle Fibre Atrophy**

Callahan (2008) stated that MV is associated with atrophy of all diaphragmatic fibre types, after as little as 18 to 69 hours of ventilation, but that the exact prevalence, time course and incidence of diaphragmatic atrophy and respiratory muscle weakness in these patients are not known (Tobin 2011: Callahan 2008; Levine et al, 2008). Immobility of the respiratory muscles, as seen with MV, causes type IIa fibres to convert to type IIb fibres which have a lower aerobic capacity than type IIa fibres (Gunderson and Bruusgaard 2008; Nava et al, 2002). The amount and density of mitochondria in the muscle fibres also decrease by half or more due to immobility (Nava et al 2002). The noticeably smaller type I and II diaphragm muscle fibres (compared to peripheral muscle fibres), during post mortem studies on rats, indicated diaphragm muscle fibre atrophy after 48 hours of controlled mechanical ventilation (CMV)

(Shanely, Zergeroglu, Lennon, Sugiura, Yimlamai, Enns, Belcastro and Powers 2002). The authors explained this phenomenon as due to the inactivity or low levels of activity of the diaphragm during CMV. Through adjustment of ventilator settings and administration of pharmacotherapy, the respiratory muscles may be rendered almost (or completely) inactive (Shanely et al, 2002). Chang, Boots, Henderson, Paratz and Hodges (2005) reported a negative relationship between ventilatory days and the respiratory muscle fatigue resistance index, which meant that if the patient was kept on CMV for longer periods; the more the respiratory muscles would be proportionally prone to fatigue.

Levine et al (2008) evaluated and compared the diaphragms of 14 brain-dead organ donors who presented with respiratory muscle inactivity and were ventilated on CMV for prolonged periods (18 to 69 hours). Biopsies of the diaphragm of the case subjects showed that both the type I and type II muscle fibres in the diaphragm were noticeably smaller than those of the control subjects (MV for 2-3 hours), which indicated fibre atrophy. The case subjects were 14 brain-dead organ donors and the eight control subjects underwent surgery for benign lesions or localised lung cancer. The specimens from the control subjects showed decreased cross-sectional areas of slow-twitch and fast- twitch fibres of 57% ($p = 0.001$) and 53% ($p = 0.01$) respectively. Levine et al concluded that 18-69 hours of complete diaphragmatic inactivity and MV resulted in marked atrophy of human diaphragm myofibers.

It is interesting to note that exposure to 18 hours of sodium pentobarbital (Nembutal) anaesthesia does not result in diaphragmatic atrophy, but 18 hours of CMV induces significant myofibril atrophy of all muscle fibres, with the Type II fibres showing a greater degree of atrophy (Callaghan 2008; Levine et al 2008). Levine et al (2008) also took biopsies of the soleus muscle in the lower limb of their study subjects during this period of patient inactivity. This was done to compare the degree of muscle fibre atrophy of the lower limb to the degree of atrophy of the diaphragm. After 18 hours of CMV, there was no loss of total body mass and no reduction in the mass of the soleus muscle compared to the loss in protein content and mass of the diaphragm. Mechanical ventilation constitutes a rather unique form of muscle “disuse” in the diaphragm in the sense that it is at the same time mechanically unloaded, electrically inactivated, and subjected to changes in myofibril length by cyclical lung inflation or PEEP (Petrof, Jaber and Matecki 2010). These results show that the removal of mechanical activity from the ever active diaphragm (24 hours a day) via CMV leads to rapid muscle atrophy and this finding was also concurred in a similar study done by Shanely et al (2002). The diaphragm is normally exposed to a negative pressure environment along its pleural surface that can serve as a stretch-like hypertrophic stimulus, which is removed by the

application of positive-pressure ventilation (Petrof, Jaber and Matecki 2010). All of these factors may help to explain the very rapid diaphragmatic atrophy and force loss observed during MV.

2.3.4 Muscle Fibre Remodelling

After two to four days of CMV the diaphragms of rats showed an increase in hybrid fibres, in the midst of both slow and fast myosin heavy chain isoforms in the same fibre, which occurred at the expense of the pure Type 1 fibres (Vassilakopoulos and Petrof 2004; Yang et al 2002; LeSouef, England, Strogryn and Bryan 1988). Therefore after two to four days of CMV the diaphragm is likely to have a decreased endurance capacity, due to a loss of type 1 fibres. This can explain the reason why the diaphragm is more susceptible for ventilator-induced diaphragmatic dysfunction and low frequency fatigue after 48 hours of CMV. During similar short periods of inactivity the muscles of the lower and upper limbs showed a shift from fast–to-slow twitch myosin profile transformation and a shift towards faster myosin profile transformation in long inactive periods (Talmadge, 2000). The duration of inactivity required for this muscle fibre remodelling in the diaphragm is much shorter than in limb muscles, making it more prone to the effects of disuse during CMV (Talmadge 2000). It is currently unclear if other modes of ventilation, such as assist-mode ventilation or synchronized intermittent mandatory ventilation with pressure support, (which require some diaphragmatic work) could be associated with different degrees of diaphragmatic dysfunction in humans (Sieck and Mantilla 2008).

2.3.5 Sub Cellular Structural Abnormalities

Structural abnormalities of different sub cellular components of diaphragm muscle fibres were found in the study on brain dead organ donors who were on prolonged MV (18 -69 hours) (Levine et al 2008). Both the slow-twitch fibres and the fast twitch fibres in the case specimens were appreciably smaller than those in the control specimens as reported section 2.3.3. However the specimens in both groups did not differ with respect to the proportions of slow- and fast-twitch fibres. The time of inactivity of the case specimens were 18 – 69 hours compared to only two - three hours in the control group. It could be speculated that the outcome of this study could have been influenced by the difference in the time of diaphragm inactivity between the two groups. The smaller muscle fibres of both slow- and fast-twitch fibres, shown in the case specimens, might lead to increased susceptibility of the diaphragm to contraction-induced injury, during uncontrolled spontaneous breathing attempts of subjects on MV (Levine et al 2008).

2.3.6 **Reduced Inspiratory Muscle Endurance**

Muscle endurance is the ability to sustain a specific muscular task over time. Endurance is an extremely complex and integrated quality of a muscle or group of muscles that is related to its resistance to fatigue. A prospective observational non-randomised control study, done by Chang et al (2005) on 20 subjects who had received MV for 48 hours or more, and had been discharged from the ICU was the first to show that inspiratory muscle endurance was reduced in patients who were successfully weaned following MV for more than 48 hours. The authors assessed muscle endurance by measuring the maximum inspiratory pressure (Pimax), following a resisted inspiratory training program of two minutes, as well as measured the fatigue resistance index (FRI) Pimax The FRI Pimax was lower after the resisted inspiratory training program; this effect was more severe in subjects who were on longer periods of ventilation. The clinical implication of this study is that specific rehabilitation programs, such as inspiratory muscle training may be indicated to improve inspiratory muscle endurance in this patient population. Patients who are mechanically ventilated, especially those with atelectasis and obstructive lung disease, and are breathing spontaneously on CPAP, have the benefit of the positive airway pressure that reduces the WOB (Pierce 2006). The same patient, when breathing on a T-piece or via a tracheal mask, is likely to demonstrate a higher WOB due to not having the benefit of the positive airway pressure. It can therefore be assumed that during CPAP ventilation mode more type I fibres (endurance) of the diaphragm will be recruited and more type II fibres (strength) during T-piece or tracheal mask mode (Pierce 2006). These theoretical principles can be used in the clinical setting to recruit, strengthen and condition the specific diaphragmatic muscle fibres that show reduced endurance or weakness.

2.3.7 **Respiratory Muscle Fatigue**

Muscle fatigue is defined as a loss of the capability to generate skeletal muscle force and/or velocity that is accompanied by recovery during rest (Supinski, Fitting and Bellemare 2001). Muscle fatigue results from the inability of the contractile and metabolic processes of the muscle fibres to continue supplying the same work output. The nerve continues to function properly and the nerve impulses pass normally through the neuromuscular junction into the muscle fibre, but the contraction becomes weaker and weaker because of the depletion of adenosine triphosphate in the muscle fibres themselves (Guyton 1977). Excess protons are released during rapid glycolysis and this is the reason for muscle fatigue during high intensity exercise, according to Noakes (1990). As exercise intensity increases, so does the rate of carbohydrate utilization until, at high exercise intensities (greater than 85% to 95% VO_{2max}.), only carbohydrate is burned. This results in an increased proton production to a rate that exceeds the rate at which protons can be transported into the mitochondria. The excess

protons combine with pyruvate to produce lactate 'glycolytic overflow'. The production of lactate exceeds the rate at which these glycolytic products can be metabolised in the mitochondria, leading to muscle fatigue during high intensity exercises (Noakes 1999).

Muscle fatigue is conveniently classified into different types; central, high frequency and low frequency fatigue (Supinski, Fitting and Bellemare 2001). The different types of fatigue represent different biophysical mechanisms of fatigue development and each type having different physiological characteristics (Supinski, Fitting and Bellemare 2001). Central fatigue refers to a condition in which muscle force generation during sustained or repetitive contractions becomes limited due to a decline in motoneuronal output. High-frequency peripheral fatigue is the failure to generate force as a result of a reduction in motor output from the central nervous system. It refers to failure at the neuromuscular junction or at a point distal to this structure (Supinski, Fitting and Bellemare 2001). This type of fatigue is reported to resolve extremely quickly (minutes) after cessation of strenuous muscle contractions (Aubier, Troyer, Samson, Macklem and Rossous 1981). Low-frequency peripheral fatigue is present when the forces generated in response to high-frequency stimulation are not impaired. This indicates that the contractile proteins are capable of generating maximum force provided that sufficient calcium is released by the sacroplasmic reticulum (Supinski, Fitting and Bellemare 2001). Low frequency fatigue does not resolve as quickly as high-frequency fatigue and can take as long as 24 hours to resolve (Supinski, Fitting and Bellemare 2001).

Excessive loading of respiratory muscles in patients who were having difficulty in weaning from MV reportedly resulted in low frequency fatigue; this effect lasted for at least 24 hours (Polkey and Moxham 2001; Laghi, D' Alfonso and Tobin 1995; Mador and Acevedo 1991). The structural abnormalities of the diaphragm muscle fibres of ventilated patients might lead to increased susceptibility of the diaphragm to contraction-induced injury and low frequency fatigue during spontaneous breathing attempts after long periods of diaphragm inactivity (Vassilaskopoulos, Roussos and Zakynthino 2006; Vassilaskopoulos and Petrof 2004; Powers 2002; Sassoon 2002; McCool, Tzelepis, Leith and Hoppin 1989). These authors concurred with and affirmed the conclusion that exercise-induced muscle injury in humans frequently occurs after unaccustomed exercises as stated by Clarkson and Hubal (2002) and Noakes (1990). If low frequency fatigue of the diaphragm and respiratory muscles occurs during weaning of MV, the added risks of ICU complications and consequential increase in cost of ICU care are significant and therefore it is recommended that low frequency fatigue should be prevented if possible.

Ventilator induced diaphragmatic dysfunction due to MV, is time-dependent, but current evidence does not distinguish the impact of other factors, involved in diaphragm dysfunction, such as patient-ventilator synchrony, underlying disease state, infection and drug therapy (Haitsma 2011). All these factors can converge with ventilatory induced diaphragmatic dysfunction to exacerbate diaphragmatic weakness in critically ill patients. It is currently not possible to definitively diagnose any patient with ventilatory induced diaphragmatic dysfunction, due to the presence of these multiple confounding factors (Petrof et al 2010).

The detrimental effects of muscle atrophy, low frequency fatigue and muscle fibre remodelling that occur in the diaphragm of patients who have been on MV for as little as 18 hours must be taken into consideration in the application of weaning strategies. At present, the best approach to prevent ventilator induced diaphragmatic dysfunction is to avoid controlled MV and neuromuscular blocking agents as far as possible and strategies or modes of MV which decrease the risk of ventilator induced diaphragmatic dysfunction and preserve diaphragmatic function should be developed (Petrof, Jaber and Matecki 2010). Alarming to note is that an increased number of patients are being discharged from the ICU to chronic care long-term ventilation facilities because of repeated failed attempts to wean from MV (Callahan 2008). It is unclear if the same trend can be detected in South Africa as chronic care long-term ventilation facilities are not readily available in South Africa, but the consequences of failed weaning, prolonged ICU stay, increased risks of complications and death are likely to be similar.

2.4 WEANING STRATEGIES IN ADULT MECHANICALLY VENTILATED PATIENTS

There is consensus among various authors (Stawicki 2007; Ambrosino 2005; Grap, Stickland, Tormek, Lubin, Keane, Dalby, Townes and Sessler 2003; Hess 2002; Hess and Branson 2000; Ely, Meade, Haponik, Kollef, Cook, Guyatt and Stoller 2001; MacIntyre 2001; Vitacca et al 2001; Esteban, Frutos-Vivar, Tobin, Alia, Salsona, Vallverdu, Fernandez, De La Cal, Benito, Carried, Macias and Blanco 1995) that 40% of the overall time spent in ICU is devoted to weaning and that approximately 20% of all patients experience difficulty in weaning. Stawicki (2007) stated that despite advances in MV and respiratory support, the science of determining if the patient is ready for extubation is still very imprecise. Reintubation rates reportedly vary from 2% to 25%, depending on the ICU population studied (Esteban et al 1995). A rate of between five and 10% has been postulated as an “acceptable” reintubation rate (Stawicki 2007; Dries, Mc Gonigal, Malian, Bor and Sullivan 2004) although it would be ideal not to have to reintubate a patient who was recently extubated. The process of weaning from mechanical

ventilator support is usually only undertaken if the underlying pathological process that prompted the commencement of MV is improved or resolved (Ambrosino 2005).

2.4.1 Predictors of Weaning Success and Extubation Failure in Weaning Strategies

Objective and subjective parameters (Stawicki 2007) are used to determine whether a patient is ready for commencement of weaning. Some of the objective parameters used to assess a patient's readiness for a spontaneous breathing trial (SBT) include:

a) level of positive end expiratory pressure (PEEP) of five to eight cm H_2O,
b) PaO_2/FiO_2 ratio above 150 to 200,
c) FiO_2 level below 0.5,
d) pH above 7.25; and
e) patient's ability to initiate spontaneous breaths.
f) respiratory rate of < 35 b/min during spontaneous breathing

The reported subjective parameters include:

a) haemodynamic stability,
b) absence of clinically significant, vasopressor-required hypotension,
c) absence of active myocardial ischemia,
d) normal or improving appearance on chest X ray,
e) appropriate neurological examination; and
f) adequate muscular strength to initiate/sustain the respiratory effort.

These subjective and objective parameters were also included in the American Association of Respiratory Care's Clinical Practice Guideline for the removal of the endotracheal tube (Wratney and Cheifetz 2007).

Evidence based clinical practice guidelines for managing the ventilator weaning process and extubation were published by Cook et al (1999) and MacIntyre, Epstein, Carson, Scheinhorn, Christopher and Muldoon (2005). Together these publications generated a list of useful weaning and extubation parameters that are still widely used. Despite high sensitivity (78% to 100%), these parameters were plagued by low specificity (11% to 36%). According to Stawicki (2007) the low specificity of these parameters could have contributed to the exclusion of some patients for weaning, who might be able to breathe independently, leading to unnecessary longer periods of MV for these patients.

Frutos–Vivar et al (2006) analysed clinical data from adults who received MV in ICU's in 37 hospitals in eight countries and found that among routinely measured clinical variables, rapid

shallow breathing index (RSBI) above 125 breaths/min/ℓ, a positive fluid balance 24 hours prior to extubation, and pneumonia at the initiation of ventilation were the best predictors of extubation failure. Tobin, Brochard and Rossi (2002) as well as Tobin and Jubran (2006) tested the reliability of the RSBI or frequency-to-tidal volume ratio (f/V_T) as a predictor of weaning success and concluded that an average sensitivity of 0.87 indicated that the RSBI was a reliable screening test for weaning success. Meade et al (2001) found that a RSBI below 100 breaths/min/ℓ, respiratory rate below 35/min, mouth occlusion pressure (100 msec after the onset of inspiratory effort divided by maximum inspiratory pressure (MIP)) of 0.3 and a MIP of above -20cm H_2O were the most promising predictors of successful trials of unassisted breathing. Rapid shallow breathing index has a strong inverse relationship to peak negative oesophageal pressure therefore reflecting the influence of muscle weakness (Kallet, Hemphill, Dicker, Alonso, Campbell, Mackenzie and Katz 2007; El-Khatib, Zeineldine and Jameleddine, 2007).

Evidence shows that the RSBI rate, a measure of change of RSBI over time, may offer more predictive value than RSBI alone (Segal, Oei, Oppenheimer, Goldring, Bushtani, Riggiero, Berger and Fiel 2010; Stawicki, 2007; Mehta et al 2000). The RSBI rate is calculated by obtaining a serial measurement of the RSBI at set intervals. The percentage difference is calculated between the initial RSBI and the subsequent RSBI (RSBI rate = $[(RSBI_2 - RSBI_1)/RSBI_1] \times 100$). A RSBI rate of less than 20% was over 90% sensitive and 100% specific for predicting weaning success in the study done by Stawicki in 2007. Segal et al (2010) found in a prospective observational study of 72 medical subjects who were extubated after MV, that a RSBI rate of more than 20% was 89% sensitive and 89% specific for predicting extubation failure. Similar values (positive predictive value of 100% and a negative predictive value of over 81%) were reported by Steier, Kaul, Seymour, Jolley, Rafferty, Mann, Luo, Roughton, Polkey and Moxham (2006) who conducted a prospective observational study of 506 subjects referred for respiratory muscle function tests. The referrals were mainly for neuromuscular diseases and dyspnoea of unknown causes.

In light of the above information, the RSBI was used as an objective predictor of readiness for a SBT in the intervention group of the current study.

2.4.2 **Assessment of Respiratory Muscle Function**

Respiratory muscle weakness is likely to be a relatively common problem in patients who receive MV. If patients develop respiratory muscle weakness, weaning might be difficult and prolonged. A tool used to assess respiratory muscle strength should ideally be both sensitive and practical in the complex ICU environment. According to Callahan, (2008) it is important to

note that the clinical tools which are generally used to assess respiratory muscle strength in mechanically ventilated patients are often inaccurate and imprecise. This is due to the fact that they are dependent on the operator and the voluntary effort of the patient (Callahan 2008).

2.4.2.1 **Respiratory muscle strength and function**

Patients with muscle weakness are less able than normal patients to compensate for minor changes in respiratory function (Moxham and Goldstone 1994). According to these authors, respiratory muscle weakness reduces vital capacity (VC) (Moxham and Goldstone 1994). In mild weakness, $PaCO_2$ is usually less than normal, implying alveolar hypoventilation. Moxham and Goldstone (1994) stated that: measurement of respiratory muscle strength in patients on MV is difficult and inaccurate. Assessment of respiratory muscle strength can be relatively simple to perform, but it is often difficult to ensure a maximal effort from the patient on MV; therefore these tests have high specificity but low sensitivity. Examples of these assessments are the maximum inspiratory mouth pressure (Pimax), maximum expiratory mouth pressure (Pemax) tests and the maximum sniff pressure test. These tests are usually performed on non-intubated subjects or need sophisticated equipment to be performed on ventilated subjects and are not readily available in the average private ICU in South Africa. Therefore these tests were not included in the current study.

Measurement of MIP has been used in the clinical setting to assess inspiratory muscle strength. The manoeuvre consists of a maximum inspiratory effort against a closed airway and requires a considerable degree of patient cooperation and coordination. The patient is asked to perform maximum inspiratory efforts for 15-20 seconds and the highest MIP generated during this period is recorded (Tobin, Brochard and Rossin 2001). A MIP of > -20cm H_2O is reportedly needed to sustain independent breathing. Maximum inspiratory pressure is difficult to measure in a reliable way in intubated patients due to various factors such as sedation, mode of ventilation, lack of motivation and understanding and decreased glucose control (Caruso, Carnieli, Kagohara, Anciaes, Segarra and Deheinzelin 2008).The use of a unidirectional valve allows MIP to be performed easily in uncooperative patients (Caruso, Denari, Ruiz, Bernal, Manfrin, Freidrich and Deheinzelin 1999). Maximal inspiratory pressure had a sensitivity of 87% and specificity of 91%, for the prediction of successful periods of unassisted breathing followed by extubation as reported in the pooled results of 65 observational studies that were assessed by Meade et al (2001). Maximal inspiratory pressure was used as an outcome measure in the current study. The Vela ventilator system (used in the test setting) instruction procedure for measurement of MIP was used. This procedure will be discussed in the methods section of this dissertation.

2.4.2.2 **Respiratory muscle endurance**

Any measurement of endurance is task specific because different tasks result in varying recruitment patterns of motor units and synergistic muscle groups, each with varying endurance qualities. There are a large variety of techniques that have been developed to measure endurance of respiratory muscle. These tests differ mainly on the type of task that is being performed. Endurance of respiratory muscles is most often defined in terms of the ability to sustain a level of minute ventilation or a level of inspiratory or expiratory pressure. These simple measurements often present limitations to evaluate the effect of the load on the respiratory muscles. The rough estimate of the level of activation of a muscle (energy requirements) is largely determined by the tension developed by that muscle over time (i.e. tension-time product) and the rate of mechanical work being performed (Clanton, Calverly and Celli 2001). Respiratory muscle endurance time can be predicted from the load/capacity ratio or endurance curves (Hart, Hawkins, Hamnegard, Green, Moxham and Polkey 2002). Endurance curves can be generated for each task by plotting the intensity of the task versus the time it can be sustained. At high intensity levels, a task can be sustained for only a few repetitions but as the task intensity is decreased the task can be sustained for longer. This is referred to as maximum sustainable task or load (Clanton, Calverly and Celli 2001).

There remains a debate on the use of non-invasive respiratory breathing to task failure to assess inspiratory muscle performance (Rohrbach, Perret, Kayser, Boutellier and Spengler 2003). This method, where a patient's respiratory system is loaded (high intensity sustained up to the point of failure) could result in low frequency fatigue of the respiratory muscles and ventilator-induced diaphragmatic dysfunction. In the American Thoracic Society/European Respiratory Society's Statement on respiratory muscle testing, Clanton, Calverly and Celli (2002) described different techniques and tests to assess respiratory muscle endurance such as pressure-time product, work of breathing, ventilatory endurance test, endurance of external loads applied to the airway, repeated maximum inspiratory pressures, maximum sustainable isoflow and the endurance of the diaphragm. According to Clanton et al (2002) most of the studies of ventilation endurance, to date, have been undertaken within a research context and not in the clinical setting. All of these tests and techniques need specific laboratory equipment and are not suitable for the general ICU setting, where such tests are not readily available and might be very costly to the patient in the private health care setting. For this reasons a specific test for respiratory muscle endurance was not included in the current study.

2.4.2.3 **Respiratory muscle fatigue**

Because muscle fatigue is such a complex phenomenon, a test that is well suited to detect one form of fatigue may be incapable of detecting another. According to Supinski et al (2001) there is no successfully developed and tested technique to permit precise identification of respiratory muscle fatigue in the clinical setting. The RSBI has been described by different authors (Byrd et al 2010; Epstein 2009; Boles et al 2007; Cohen, Shapiro, Grozovski, Lev, Fisher and Singer 2006; Frutos-Vivar et al 2006; Aboussouan, Lattin and Anne 2005; Ambrosino 2005; Dries et al 2004; Ely et al 2001; Aldrich, Karpel, Uhrlass, Sparapani, Eramo and Ferranti 1989) as the most clinically suitable test, but it can not be considered a specific marker of fatigue. A single measurement of force is inadequate to detect fatigue: rather, muscle force generated or force capability must be demonstrated to decrease during a series of measurements over time. The RSBI rate described in section 2.4.1 of this chapter (Segal et al 2010; Stawicki 2007; El-Khatib, Zeineldine and Jameleddine 2007; Steier et al 2006) can be used as an indicator of respiratory muscle fatigue during weaning. For that reason the RSBI rate was included in the intervention group of the current study.

Respiratory muscle function tests in ICU have the greatest application in the prediction of weaning outcome. The majority of these measurements require considerable attention to detail and are not useful in the clinical setting and are therefore restricted to research settings (Stawicki 2007; Tobin et al 2002).

It can be concluded that any assessment tool used to evaluate the strength, endurance or fatigue of the respiratory muscle of a patient on MV should be specific and sensitive. The use of one test alone can over-diagnose muscle weakness; therefore a combination of different tests informs the diagnosis of respiratory muscle weakness, decreased endurance or muscle fatigue. The consensus document of the sixth international consensus conference on intensive care medicine supports a daily screening of weaning readiness through the use of a SBT (Boles et al 2007). The implication is that a SBT improves lung function and therefore improves weaning success. These studies indicate that health care practitioners are in general poor in subjectively recognizing readiness to wean. The use of a SBT may also stop unnecessary sedation.

2.4.3 **Spontaneous Breathing Trial**

When spontaneous breathing is maintained during MV, improvements in pulmonary gas exchange, systemic blood flow and oxygen supply to the tissues have been observed, which reflects in the clinical improvement of the patient's condition (Putensen, Muders, Varelmann

and Wrigge 2006). Early spontaneous breathing during MV counteracts the adverse cyclic alveolar collapse in dependent lung regions and may eventually result in decreased duration of MV, ICU length of stay and overall medical cost (Putensen et al 2006). A prospective study of 488 subjects, done by Robertson (2007) in an academic surgical ICU with 547 MV episodes reported that a daily SBT of 30 minutes improved the extubation rates by 42% without a change in the reintubation rate. The Mc Masters University evidence-based clinical practice guidelines states that a SBT, lasting from 30 minutes to 120 minutes, may establish the patient's ability to be liberated from the ventilator (Ely et al, 2001). This clinical guideline reviewed 1000 articles from 1971 – 2000 and included 154 articles for final review and evaluation. Tolerance of a SBT can be judged by the respiratory pattern, level of patient comfort (Putensen et al 2006), adequate gas exchange and haemodynamic stability of the patient. Multiple authors (Stawicki 2007; Ambrosino 2005; Grap et al 2003; Ely et al 2001; MacIntyre et al 2001; Vitacca et al 2001; Esteban et al 1995) cite extubation success rate of 60 - 80% in patients who passed a SBT and the general trend is to withdraw permanent ventilatory support if the patient can tolerate a SBT. In a prospective study of 217 subjects receiving MV, Vallverdij et al (1998) compared the use of a T-tube versus pressure support ventilation during a two hour SBT. They reported that the percentage of patients failing the SBT was significantly higher in the T-tube group (22% vs. 14%) (Vallverdij et al 1998). The authors speculated that the WOB on a T-tube is much higher than on pressure support ventilation due to the inspiratory pressure support supplied to a patient's airways with pressure support ventilation. Many might argue that any form of pressure support is a form of supported ventilation and that might be the reason that more patients failed the SBT on the T-tube compared to the pressure support ventilation in the study done by Vallverdij et al (1998).
If the work done by Chang et al (2005) is taken into consideration it can be assumed that the patients who failed the SBT on the T-tube might have had decreased respiratory muscle endurance and developed low frequency fatigue of the respiratory muscles. Change et al (2005) showed that patients who were on MV for longer than 48 hours had reduced inspiratory muscle endurance that worsen with the duration of MV.

Managing the patient, who fails the SBT, is one of the biggest challenges facing the ICU clinician (MacIntyre et al 2007). These patients should be placed on a non-fatiguing, comfortable form of ventilatory support that reduces the risk of ventilator-induced diaphragmatic dysfunction during the recovery period after low frequency fatigue of the respiratory muscles.

A SBT should be performed every 24 hours only if the acute disease stage has been resolved, the reason for the SBT failure has been identified and corrected and the patient is haemodynamically stable and meets the SBT requirements (Boles et al 2007; Grap et al 2003; Esteban et al 1995). This method has also been associated with more rapid weaning (Begany 2002).

No clear guidelines on how to prevent the risk of ventilator-induced diaphragmatic dysfunction, the prevention of diaphragmatic fatigue or the mechanical ventilator support management in the spontaneous breathing stage of MV, could be found. There is still controversy on how a SBT should be performed, and studies failed to show any significant difference between a SBT duration of 30 and 120 minutes, CPAP of 5cm H_2O versus T-piece for an hour and CPAP of 7cmH_2O vs T-piece (Boles et al 2007; Stawicki 2007; Mac-Intyre et al 2002). Cohen et al (2006) compared the use of automatic tube compensation (ATC) mode and CPAP during a SBT. Automatic tube compensation is a ventilation mode that provides pressure support ventilation based on the tube size and inspiratory flow. The WOB of a patient ventilated with ATC should theoretically be the same as when extubated (Cohen et al, 2006). Patients on ATC mode tolerated the SBT better than the CPAP group (96% vs. 85%; p=0.08) and the rate of reintubation in the ATC mode group was 14% compared to 24% in the CPAP group. Unfortunately ATC mode is not available on all brands of ventilators and could not be used in the current study. The findings of Cohen et al (2006) is strongly suggestive that in CPAP mode there might be inadequate support when inspiratory flow is low or that over-assistance is given when inspiratory flow is high resulting in more patients failing a SBT on CPAP mode. It is therefore important that a SBT or spontaneous breathing episodes on CPAP mode should be well managed to ensure that the patients get adequate support (not under-or over-assistance) to prevent low frequency fatigue and/or ventilatory diaphragmatic injury during a SBT or spontaneous breathing episodes. This was taken into consideration in the development of the individualised CPAP program in the current study.

Stawicki wrote in an overview of weaning and extubation that the proposed method to determine if a patient failed or tolerated a SBT should combine objective and subjective indicators as listed below (Stawicki 2007):

a) Inadequate gas exchange indicated by any of the following:
   Arterial oxygenation saturation (SaO_2) lower than 85% to 90% for longer that five minutes, PaO_2 lower than 50 to 60mmHg, a pH lower than 7.3 and/or a increase in $PaCO_2$ > than 10mmHg.

b) Unstable ventilatory/respiratory pattern for longer than five minutes indicated by:
A respiratory rate above 30 to 35 breaths/minute and/or a 50% increase in the subject's average respiratory rate.

c) Haemodynamic instability for longer than 30 minutes indicated by any of the following:
A HR above 120 to 140 beats/minute, HR changes greater than 20% of the base line of the patient, systolic BP above 180mmHg or lower than 90mmHg and/or BP changes greater than 20% of the baseline of the patient or if the patient requires vasopressor therapy.

d) Change in mental status i.e. coma, agitation, anxiety and/or somnolence.

e) Signs of increased WOB like nasal flaring, paradoxical breathing movements or the use of accessory respiratory muscles; and

f) Onset of worsening discomfort with or without diaphoresis.

Well-defined, structured weaning protocols, independent of the ventilation mode used, resulted in better outcomes than uncontrolled clinical practice (MacIntyre 2007; Ambrosino 2005; MacIntyre 2005; Grap et al 2003; Ely et al 2001; MacIntyre et al 2001: Vitacca et al 2001; Esteban et al 1995). Investigators and clinicians should not expect any predictors of weaning or extubation to be particularly powerful on their own. When predictors of weaning are incorporated in formal weaning protocols they retain their full predictive power and these protocols should then perform better than usual clinical care (Meade et al, 2001).

2.4.4 **Weaning Protocols**

A systematic review of randomised control studies was conducted by MacIntyre et al (2000) for the Agency for Healthcare Policy and Research (AHCPR). One of the recommendations made (Grade A) was that non-physician health care practitioners be used in the ICU to enhance patients' weaning and extubation. Begany (2002) stated in an editorial that the use of non-physician led protocols can decrease the average stay in ICU by two days and halve the complication rate. Grap et al (2003) compared the duration of MV of 469 subjects (control group) before a non-physician led weaning protocol was implemented to that of 459 subjects (intervention group) after the protocol was implemented in an open medical ICU setting. They reported a significant reduction in the duration of MV in the group managed with the non-physician led protocol. A prospective randomised controlled study on 299 subjects compared the outcomes of a physician-directed weaning protocol to that of a non-physician health care practitioner led protocol in a medical ICU (Krishnan, Moore, Robeson, Rand and Fessler 2004). The authors reported no significant difference in the patient characteristics between the

two groups and concluded that protocol-directed weaning may be unnecessary in a closed ICU with generous physician staffing and structured rounds.

Dries et al (2004) concluded that the use of protocol-driven ventilator weaning strategies reduced the duration of MV and occurrence of ventilator-associated pneumonia (VAP). Patients with trauma and those after general surgery showed a reduction in complications and the number of patients failing extubation was reduced from 43 to 25 in a patient population of 295 over a two year period. This was a survey done before and after the implementation of a protocol-driven ventilator weaning strategy.

In 2001 a collective task force, led by MacIntyre, facilitated by the American College of Chest Physicians, the American Association for Respiratory Care and the American College of Critical Care Medicine drew up evidence–based guidelines for weaning and discontinuation of ventilatory support (MacIntyre et al, 2002 & 2001). Some of the recommendations from the guideline document that are relevant to the current study include:
Recommendation 1: Reversal of all possible ventilatory and non-ventilatory issues that may affect weaning outcome should be an integral part of the weaning process.
Recommendation 2: Patients who receive MV for respiratory failure should undergo a formal assessment of discontinuation potential if they meet certain set criteria.
Recommendation 3: Formal discontinuation assessments for patients receiving MV should be performed during spontaneous breathing rather than while the patient is still receiving substantial ventilatory support.
Recommendation 4: Patients who failed a SBT should be assessed to identify and correct the causes as soon as possible.
Recommendation 5: Patients who failed a SBT should receive a stable, non-fatiguing, comfortable form of ventilatory support until fatigue is reversed.
Recommendation 6: Weaning /discontinuation protocols that are designed for non-physician health care professionals should be developed and implemented in ICU's.
Recommendation 12: Weaning strategies in the patient that is on prolonged MV should be slow-paced and should include gradually lengthening self-breathing trials.

According to Cohen et al (2006) the successful, timely weaning and extubation of critically ill patients has a considerable impact on ultimate outcome. Prolonged MV (longer than 48 hours) as well as untimely premature extubation resulting in extubation failure and reintubation, is strongly linked to increased morbidity and mortality.

According to the above mentioned recommendations and the evidence presented in this literature review, protocol driven weaning strategies are likely to provide adequate support without compromising the patient's overall condition. It is recommended that a formal weaning assessment with defined weaning criteria and a SBT should be part of such a protocol driven weaning strategy (Heunks and Van Der Hoeven 2010; Stawicki 2007). The use of non-physician driven protocols, administered by registered nurses, physiotherapists/ respiratory therapists, seems to result in better outcomes and lower reintubation rates than other weaning strategies (MacIntyre et al 2002 and 2001).

2.4.5 Multi-Disciplinary Team Model in the Weaning Strategies of Patients on Mechanical Ventilation in ICU

The multidisciplinary team model for ICU care reduces mortality, ICU length of stay, complications and cost of care (Garrubba, Turner and Grievenson 2009; Durbin, Abraham and Terjung 2006). The essence of this model is that a dedicated multidisciplinary team, consisting of at least an intensivist, ICU trained nurses, pharmacist and a respiratory therapist or physiotherapist, should provide clinical care to patients in ICU's. If the scientific evidence that supports the positive impact of clinical practices of several of the ICU specialists is taken into consideration, then it seemed obvious that a team of these experts continually present at the patient's bedside would provide the best possible patient outcomes (Durbin 2006; Brilli, Spevetz, Branson, Campbell, Cohen, Dastam Harvey, Kelly, Kelly, Rudis, St Andre, Stone, Teres and Weled 2001; Stiller 2000).

The ICU is a nexus for interspeciality and interdisciplinary tensions because of its pivotal role in the care of the most critically ill patients of a hospital. The use of non-physician driven weaning protocols was one of the strongest recommendations of the AARC (2001) but interprofessional tension has been documented in several clinical domains such as the ICU (Lingard, Espin, Evans and Hawryluck 2004). It can threaten the delivery of quality health care and the implementation of evidence based clinical guidelines (Chan et al 2001). Learning how to obtain results collaboratively is a critical aspect of professional competence to achieve daily clinical goals and to delineate professional boundaries (Lingard et al 2004). To foster optimum team function, the forces governing the interactions between professions and between specialities must be understood (Lingard et al 2004). Lingard et al (2004) found that the "team", in ICU, is not a unified body but rather a complex and fluid entity composed of core and expanded groups. Membership of these groups is continually negotiated on the basis of relative professional roles, immediate needs and unspoken rules of play. Understanding these rules can aid in the implementation of new protocols.

Two dominant mechanisms in the ICU multi-disciplinary team were described namely (a) perception of ownership, which can be perceived as either collective (i.e. ownership by the ICU team) or individual (ownership by a professional or a profession). Shared perception of collective ownership of the patient's wellbeing was portrayed as the foundation of the ICU multi-disciplinary team's identity; (b) process of trade is instances in which team members' trade valued commodities as they negotiate their collaborative work. This could involve concrete, physical commodities (equipment and resources) and abstract, social commodities (respect, goodwill and knowledge). Lingard et al (2004) concluded that the forces of ownership and trade have a central role in the daily negotiations that constitute teamwork in the ICU setting. If ignored, tension accumulates and collaboration becomes sluggish. The quality of care of the critically ill patients will improve if this is understood and correctly managed. Engaging the multidisciplinary team in a clinical protocol change would be an important factor to determine the successful implementation of and adherence to such a protocol (McLean et al 2006).

To ensure a successful outcome, all of the above were taken into consideration when the new protocol for weaning of mechanically ventilated patients was introduced in the multi-disciplinary ICU setting for the current study.

2.5 PRINCIPLES OF MUSCLE REHABILITATION

The main focus of the research question is the effectiveness of the implementation of an individualised CPAP program during the spontaneous breathing stage of a weaning protocol for adult patients on MV. This CPAP program used in this study utilised the following three principles of muscle rehabilitation.

2.5.1 Specific Adaptation to Imposed Demand

The aim of any training program is to adapt the individual to the demands of the required task performance. The conditioning program should be task-specific and tailored for the individual. The speed, intensity and type of contraction will cause specific adaptation to the imposed demand in the muscle fibres and fitness levels (McArdle, Katch and Katch 1996). Exercising at sub-maximal levels for a lengthy period will recruit only type I ST fibres, and high-intensity brief bouts of training will recruit type II FT fibres (Brukner and Khan 2009). In type I muscle fibres the major adaptation occurs at the mitochondrial level, with an increase in size and composition resulting in improved metabolism and ATP production (Grobler, Collins, Lambert, Sinclair-Smith, Derman, St Clair Gibson and Noakes 2004). In type II fibres the adaptation is seen in the glycolytic pathway by increasing the activity of glycolytic enzymes and also

increasing the ability of the muscle fibres to continue to perform despite a low intracellular pH. Mitochondrial enzyme activities remain unchanged in type II fibres. An exercise regime will elicit a distinct pattern of local adaptations only in trained muscles (Sutton 2007; Gibala, Little, Van Essen, Buromaster, Safdar, Raha and Tarnopolsky 2006).

2.5.2 **Overload**

A muscle must be overloaded in order to gain increases in strength, power or endurance. During training muscles are constantly broken down and resynthesized. Muscle fibres will show specific adaptation to imposed demands and stimulus, specific to that demand or stimulus and hence become more efficient. Exercise at intensities higher than normal will induce a variety of highly specific adaptations to that muscle that will enable the muscle to function more efficiently. With time, adaptation of the muscle fibres will reach a plateau if the stimulus stays the same; to overcome this, the stimulus must be increased (McArdle et al 1996). To maximize the overload principle the frequency, intensity, type and time of the stimulus must be increased throughout the exercise programme. The adaptation made through training stimulus may be lost if the stimulus is discontinued. Overload can be achieved by manipulation of frequency, intensity and duration with focus on exercise mode (McArdle, et al 1996).

2.5.3 **Individual Differences Principle**

Many factors contribute to individual variations in the training response. The relative fitness level at the start of training will have a major influence on the individual's response to any form of training. Optimal training benefits occur with exercise and training programs that are geared towards individual capacity and the needs of the participants (McArdle et al 1996).

All three principles of rehabilitation (specific adaptation to the imposed demand, overload and individual difference principles) should be included in a muscle conditioning program to achieve the maximum benefit for the patient. Training at sub maximal effort for lengthy periods will recruit type I ST fibres and high intensity bouts will recruit type II FT fibres. Muscle fibres must be overloaded to induce a variety of highly specific adaptations to that muscle that will enable the muscle to function more efficiently. Training programs must be geared towards individual capacity of the participant.

Therefore the training of the respiratory muscles of critically ill patients on MV should follow the same principles. It is the opinion of the researcher that spontaneous breathing while on the ventilator (CPAP) may recruit type I ST (endurance) fibres of the diaphragm and other respiratory muscles. To prevent low frequency fatigue the training period of muscle with compromised endurance, as seen in patients on prolonged mechanical ventilation, should

therefore not exceed the sub maximal (75%) effort of the individual. Periods of breathing on a T-piece, which recruit more type II FT fibres, should also be introduced, but should not exceed 75% of the individual's effort to prevent low frequency fatigue of the respiratory muscles. The duration of the "training" period should be progressed daily (overload) to allow for adaptation of the muscle fibres to enable the respiratory muscles to become more efficiently without causing low frequency fatigue. These two rehabilitation principles should be used in the spontaneous breathing stage of patients on MV taking the third principle of rehabilitation (individual difference principle) into consideration by gearing it towards the individual capacity, needs and progress of the subject.

2.6 MUSCLE CONDITIONING

According to Brukner and Khan (2009) muscle conditioning can be divided into four categories namely:

a) muscle activation and motor re-education,
b) muscle strength training,
c) muscle power training and
d) muscle endurance training.

These categories will be discussed briefly.

2.6.1 Muscle Activation and Motor Re-Education

Injury causes pain and swelling which have an inhibitory effect on the muscle's ability to contract. Lack of flexibility in muscles and muscle groups may prevent the correct execution of a particular movement. As discussed in section 2.3, prolonged MV causes the exact same effects on the respiratory muscles and the diaphragm (Sieck et al 1996)

Different strategies to improve motor re-education and muscle activation such as localized strengthening initially in isolation, verbal feedback, tapping, biofeedback and palpation can be used (Prentice 2004). These strategies are however not practical for patients on MV and were not included in this study.

2.6.2 Muscle Strength Training

Strength training is used to enhance exercise performance, reduce injuries and to re-establish strength that has been lost due to injury or illness (Brukner and Khan 2009).Strength is the muscle's ability to exert force and is dependent on five biochemical and physiological factors that are all stimulated by conditioning (Noakes 1999):

a) increased glycogen and protein storage in muscle by improving the glycolytic pathways,
b) increased vascularisation,

c) biochemical changes affecting the enzymes of energy metabolism,

d) increased number of myofibrils. Strength can be gained rapidly before hypertrophy occurs and therefore it appears that initial strength improvement is related to increased neuromuscular facilitation. Forceful muscle activity causes the muscle size to increase by increasing the individual type II muscle fibres and also the total number of myofibrils within the muscle fibre. No new myofibrils develop unless the muscle contracts to at least 75 % of its maximum tension (Guyton 1977); and

e) recruitment of neighbouring motor units.

The daily adjustable progressive resistive training program (DAPRE) used by athletes and bodybuilders such as DeLorme and Oxford methods are well known and well researched strength training methods (Kean, Geringer and James 2005). Progressive training can be performed in an ascending pyramid fashion (DeLorme) or a descending pyramid fashion (Oxford). The athlete will establish his/her 10 repetition maximum (10RM) by determining the maximum weight that can be lifted 10 times before fatigue ensues. The DeLorme method will start with 50% of 10RM, followed by a set of 75% of 10RM and then a set of 100% of 10RM, with rest periods between each set. The Oxford method will start with 100% of 10RM and descend to 75% and then 50% of 10RM with rest periods between each set (Kean, Geringer and James 2005; Fish, Krabak, Johnson-Greene and DeLateur 2003; Matveyev et al 2003).

The abovementioned strength training principles could be applied to the rehabilitation of the diaphragm and respiratory muscles of patients on MV. This method allows for maximal adaptation of the mitochondria of the type I muscle fibres of the diaphragm by adding daily increased progression (DeLorme) in the form of time that the patient spends on the individualised CPAP programme in each session.

2.6.3 **Muscle Power Training**

Muscle power is the ability of the muscle to work at a specific rate with a specific load, therefore strength and speed combined. This can be achieved by doing faster repetitions with the same resistance or load (Brukner and Khan 2009). Breathing harder and faster may lead to hyperventilation which is not desirable for patients on MV. Such type of breathing exercises is therefore not applicable in the rehabilitation of the diaphragm of patients on MV; therefore it will not be discussed further.

2.6.4 **Muscle Endurance Training**

Muscle endurance is the muscle's ability to sustain contraction or perform repeated contractions. Endurance type exercise recruits type I muscle fibres and the major adaptation occurs in the mitochondria. To gain endurance it is necessary to stress the aerobic pathways to improve oxidative enzyme capacity of the ST muscle fibres, particularly of those enzymes in the Krebs' cycle and the respiratory chain (Appendix 1: *Figure 1.1*) (Noakes 1999) and increase the density of mitochondria in the muscle fibres (Brukner and Khan 2009). This requires high repetition, low load exercise. Such exercise stimulates cellular adaptation and facilitates strength gains. The muscular endurance response to training only occurs in the specific muscle used in the exercise; there is no cross-over effect. The effect of endurance training on skeletal muscle metabolism according to Noakes (1999) is:

a) improved capacity of oxygen (O_2) consumption by the mitochondria; and
b) improved glycogen storage capacity and metabolism during exercise at all workloads.

The effect of sub maximal, endurance training (75% to 80% of maximum) has been described in different studies on healthy- as well as critically ill individuals (Brukner and Khan 2009; Baar 2006; Porszasz, Emtner, Goto Somfay, Whipp and Casaburi 2005; Noonan and Dean 2000; Dudley, Abraham and Terjung 1982). The major adaptation to sub maximal exercise (75% to 80% of maximum) occurs at the mitochondrial level of the muscle fibres, with an increase in size and composition with improved metabolism. This leads to improved efficiency in the tricarboxylic acid cycle (Krebs cycle) and increased ATP production.

An observational non-randomised controlled study on 15 subjects during acute respiratory failure and in 49 subjects during recovery from acute respiratory failure, done by Rosario, Sassoon, Chetty, Gruer and Mahutte (1997) found that despite a reduced mechanical load on the respiratory muscles and relatively adequate inspiratory muscle strength, subjects who failed to wean had a breathing pattern similar to that during acute respiratory failure, suggesting that they might lack muscle endurance.. Endurance training programs for the diaphragm, in patients who are mechanically ventilated, are reported to be the most appropriate training strategies, due to the physiology of the diaphragm (Rosario et al 1997). The diaphragm operates mostly at sub maximal force level and endurance training results in significant improvements in the oxidative capacity of mostly type I ST fibres (Heunks and Van Der Hoeven 2010; Powers, Criswell, Lieu, Dodd and Silverman 1992). Rosario et al (1997) suggested that these strategies may facilitate weaning.

2.6.5 **Recovery and Rest**

Doing 'too much too soon' is a common error in muscle conditioning. There is a limit on how much overload muscle fibres can tolerate before they break down and risk injury. Too much overload will cause muscle fibre damage and fatigue and too little overload will result in no or little improvement and ultimately regression (Bishop, Jones and Woods 2008; LeMura et al 2004). Although this study was performed on healthy individuals it would be reasonable to conclude that similar findings may be found for the diaphragm and respiratory muscles of deconditioned subjects, such as patients on MV. Physical work causes muscle tissue breakdown (micro trauma) and a decrease in muscle glycogen (Quinn 2008). It is therefore essential that there are enough rest periods to allow for recovery of the respiratory muscles of MV patients during stage 3 of MV to prevent muscle fatigue (Bishop, Jones and Woods 2008; Romer and Polkey 2008).

Based on the information above, the rest periods incorporated into the individualised CPAP programme for the current study were adjusted daily in a descending manner to ensure that the adaptation of the muscle fibres achieved by the increased workload of the ascending individualised CPAP programme progression did not reach a plateau.

2.7 **EXERCISE PRESCRIPTION FOR ACUTELY ILL PATIENTS**

Consistent periods of inadequate sleep, infection, sepsis and constant pain may result in subtle hormone changes that may affect muscle recovery. These hormonal changes may increase cortisol levels, decrease human growth hormone levels (active during tissue repair) and decrease glycogen synthesis. Sleep deprivation or inadequate rapid eye movement (REM) sleep as seen in intensive care patients might therefore add to lower aerobic endurance and increased ratings of perceived exertion (Quinn 2008). Many factors, including infection/sepsis, malnutrition and hyperglycaemia contribute to muscle weakness in acutely and critically ill patients (Callahan 2008; Sassoon 1990). The energy required for the synthesis of proteins from amino acids and the replication of deoxyribonucleic acid (DNA), as seen in muscle cells during training, are provided by ATP. Within the Krebs's cycle, ATP is derived from the breakdown of glucose, fats and proteins (Campbell, Reece, Urry, Cain, Wasserman, Minorsky and Jackson 2008) (Appendix 1: *Figure 1.2*). It is therefore important that the dietary requirements of critically ill patients are well managed to enable them to benefit from any training program of the respiratory and skeletal muscles.

Sub-maximal intensity training (60- 75% of maximum) provided by physiotherapists appears to have greater applicability (Noonan and Dean 2000) in this patient population due to the fact that they have a lower aerobic capacity and muscle weakness.

2.8 RESPIRATORY MUSCLE TRAINING IN MECHANICALLY VENTILATED PATIENTS

There is evidence that suggests that the inclusion of inspiratory muscle strength training during or following prolonged MV could have positive effects on inspiratory muscle function (Moodie, Reeve and Elkins 2011; Collins, Langbein, Fehr, O'Connell, Jelinek, Hagerty, Edwards, Reda, Tobin and Lagni 2008; Witt, Guenette, Rupert, Mckenzie and Sheel 2007; Taylor, Dodd, Shields and Bruder 2006; Chang et al 2005; Caruso et al 2005; HyuanSoo and WhaSook 2005; Cirio, Piaggi, De Mattia and Nava, 2003; Aldrich and Spiro 1995; Aldrich et al 1989). Inspiratory muscle strength training combined with progressive spontaneous breathing periods in mechanically ventilated patients showed a rapid increase in inspiratory muscle strength pressures that suggests neural adaptations to training (Martin, Davenport, Franceshi and Harman 2002). Martin et al performed an experimental study on 10 consecutive patients who had failed to wean from MV by conventional methods. Their protocol consisted of daily inspiratory muscle strength training through a Threshold® inspiratory muscle trainer. This was combined with daily progressive spontaneous breathing periods. After 44 days of training, nine of the 10 patients were weaned from MV (Martin et al 2002). It could be argued that the inspiratory muscle training and/or the daily progressive spontaneous breathing periods could have been the reason for their results. Neural adaptation or altered motor unit recruitment could explain the fact that type I muscle fibres in endurance muscles can perform better through repeated bouts of exercise (repeated bout effect) (Clarkson et al 2002). These results indicate that an inspiratory muscle strength training protocol combined with a progressive spontaneous breathing period aids successful weaning.

No randomised controlled studies or case studies could be identified that studied the effects of progressive spontaneous breathing periods alone on the outcomes of mechanically ventilated patients. Progressive periods of spontaneous breathing periods (Recommendation 12) form part of the evidence- based guidelines of The American Association for Respiratory Care for weaning and discontinuation of ventilatory support (MacIntyre et al 2002).

2.9 SUMMARY

The available evidence suggests that MV for periods from 18 -69 hours has detrimental effects on the respiratory muscles and especially on the diaphragm even though the prevalence, time course and incidence of diaphragmatic atrophy and respiratory muscle weakness on these patients are not currently known. It is recommended that MV should be discontinued as soon as possible to prevent added complications and additional risks to this critically ill patient population. Non-physician driven weaning protocols that involve the whole ICU team have been recommended. The spontaneous breathing stage of a mechanically ventilated patient can be seen as a rehabilitation and conditioning stage for the respiratory muscles due to the

fact that it involves more muscle activity than the full ventilation or weaning stages of MV. Therefore the same principles that apply to any other forms of rehabilitation and conditioning could be incorporated into this stage of weaning. Endurance muscles such as the diaphragm, already weakened from MV and other factors, may be rehabilitated with caution to prevent low frequency fatigue during the spontaneous breathing trial stage of weaning. Sufficient rest and recovery periods may be included to enable the respiratory muscles to adapt to the added stimuli and become more efficient. It is recommended that a spontaneous breathing program be progressed daily, to enable adaptation in strength and endurance of all the muscle fibres of the diaphragm and the respiratory muscles. Programs should be adapted to the individual patient's initial parameters and response to the conditioning program.

In the clinical setting many patients on MV are still managed without a set of predetermined scientific screening procedures for weaning readiness or a systematic weaning protocol for termination of MV. Weaning is often done according to the preference, subjective evaluation and experience of the attending physicians or nursing staff and not according to the patient's individual capability. In light of the findings in the literature review the researcher decided to apply principles similar to rehabilitation to the spontaneous breathing stage (stage 3) of patients who are mechanically ventilated to investigate its effects on the preparation of such patients for extubation.

The next chapter will explain the methodology applied in the development and implementation of an individualised CPAP programme for patients on prolonged MV in a rural private ICU setting in order to answer the research question.

CHAPTER 3

3. METHODOLOGY

The research question was: Could the implementation of an individualised graded CPAP program, during the spontaneous breathing stage of a weaning protocol, improve the preparation of a patient for extubation and therefore improve the outcomes of weaning and extubation in adult ventilated patients?

The methodology used to answer this question is discussed in this chapter and is based on the findings of the literature review in chapter 2. The study design, sample population, hypotheses tested, outcome measures, data collection procedure and instruments used are discussed in detail. Ethical considerations are addressed towards the end of this chapter and the methods used for data analysis are given at the end.

3.1 STUDY DESIGN

An experimental, prospective, non-randomised, sequential study was conducted to determine the effect of an individualised CPAP programme during stage 3 of MV (spontaneous breathing stage) on the weaning outcomes of adult patients who were mechanically ventilated for longer than 48 hours. Group one was the control group (n = 24) and group two was the intervention group (n = 24). The rationale behind the choice of this design was discussed in chapter one, as well as for the following practical reasons in the test setting:

a) due to the nature of the intervention it was impossible to blind the physicians, nursing staff, researcher and research assistants involved in the implementation of the protocol;

b) the nurse subject ratio of 1:2 made it potentially difficult to have a randomised controlled design as one nursing staff member may have had to manage two subjects that may have been in two different groups during his/her shift. Thus there was the potential for contamination of data, as well as spill over of the intervention protocol into the control group.

3.2 SUBJECTS

3.2.1 Sample Selection and Demographics

Adult subjects of both genders, who were on MV for longer than 48 hours, in the period December 2008 to November 2009 were consecutively recruited from the ICU of Cosmos Life Health Hospital, Witbank, Mpumalanga, South Africa.

Group one was the control group that received the standard weaning program and group two was the intervention group that received the intervention (individualised CPAP) weaning program.

Subjects in both groups received standard physiotherapy care that included chest clearance techniques and suction (with saline lavage) as well as passive and active range of motion movements of the limbs. No additional strengthening exercises of the limbs or respiratory muscles were performed on any of the subjects in the two groups, as this did not form part of standard physiotherapy care at the time of the study.

3.2.2 **Inclusion Criteria**

The following subjects were considered for inclusion in this trial:

a) adult male or female subjects, aged from 18 to 60 years. The age group was chosen due to the fact that 95% of the normal patient population in the research setting are from 18 to 60 years of age.

b) subjects on MV for more than 48 hours before proceeding to stage 3 (spontaneous breathing stage) of MV,

c) subjects intubated via endotracheal or tracheal tube.

3.2.3 **Exclusion Criteria**

The following subjects were excluded from this trial due to the reasons listed:

a) To ensure that the samples chosen were as similar as possible, subjects who required specific modes or strategies of MV due to their pathology/injuries were excluded from the study. This included: (i) subjects with closed or open head injuries as they are normally sedated for longer periods of time, and ventilated and weaned according to recovery of their neurological status; (ii) subjects with spinal cord injuries as they could have respiratory muscle weakness or paralysis dependent on the level and extent of their spinal lesion; (iii) subjects with critical illness polyneuropathy (CIP) or critical illness myopathy (CIM) as they tend to develop sudden loss of motor function during the course of the disorder. The loss of motor function could involve the phrenic nerve which is a major cause of difficulty in weaning from the ventilator (Schweickert and Hall 2006; Latronico, Peli and Botteri 2005). There was, at the time of this study, no method available to confirm a diagnosis of CIP or CIM (Latronico et al 2005) and the exclusion of these patients were based on the clinical signs and symptoms of CIP or CIM. These included sudden severe loss of motor function or generalised muscle weakness; flaccid quadriplegia predominant distally; mainly motor- but also sensory loss;

b) subjects with cardiac dysfunction that was not well-controlled through medication;

c) subjects on neuro-muscular blockers as neuro-muscular blockers have been reported to cause muscle weakness (Tripathi and Hunter 2006) and

d) subjects who were previously in the control croup and were later readmitted into the ICU on MV.

3.2.4 Sample Size Calculations

The clinical data of all subjects, mechanically ventilated from 1 May 2008 to 31 June 2008, was retrospectively captured to establish a trend in the unit from which the study would be conducted. (Appendix 2: *Baseline Data Collection Sheet).* This information was used by the statistician, of the Medical Research Council of South Africa, to determine the average time spent in stage 3 of MV of each patient in the adult ICU in Cosmos Hospital prior to the start of this research study. The mean time spent in stage 3 of MV during this time was 69 hours.

A sample size of 24 subjects in each group was calculated at alpha of 5% to yield 90% power to detect a clinically relevant difference of at least 24 hours in stage 3 of MV, under the assumption that the standard deviation (SD) is 20 hours.

3.3 HYPOTHESIS

The implementation of an individualised CPAP programme during stage 3 (the spontaneous breathing stage) of a weaning protocol will improve the preparation of a patient for weaning and extubation and therefore improve the outcomes (successful stage 3 of MV, successful extubation and decreased mortality rate during MV) more so than the standard weaning procedure in adult subjects who are mechanically ventilated.

3.4 NULL HYPOTHESIS

The implementation of an individualised CPAP programme during stage 3 (the spontaneous breathing stage) of a weaning protocol will not improve the preparation of a patient for weaning and extubation and therefore will not improve the outcomes (successful stage 3 of MV, successful extubation and decreased mortality rate during MV) compared to standard weaning procedures in adult subjects who are mechanically ventilated.

3.5 OUTCOME MEASURES

Primary Outcomes

- Time (in hours) of MV in stage 3 (identified from the first hour in which the subject was on spontaneous breathing on MV until extubation and/or failure to sustain stage 3 and therefore put back onto a previous stage of MV).

- Failures of spontaneous breathing during MV. (Stage 3) failures: Failure in this stage was identified at any circumstance that led to him/her being put back onto a previous stage of MV due to the inability to cope with spontaneous breathing.
- Mortality of the subject while in stage 3 or during the first 48 hours after extubation (stage 4).

Secondary Outcomes

- Successful extubation (stage 4) defined as the extubation or extubation, thus extubation or liberation without the need for reintubation for 48 hours or longer.
- Time (in hours) of MV in stage 2 (identified as the first hour of reduced MV support of either the $Fi0_2$, RR, PS or PEEP, until progressing to stage 3 or being put back on stage 1 of MV)
- Total MV Days defined from the first 24 hours of MV into the unit until extubation, transfer or death of the subject.

3.6 VARIABLES

Dependent variables	Total number of hours spent in stage 3 of MV
	Total number of hours spent in stage 2 of MV
	Total days on MV
	Failure rate of the patient's ability to sustain spontaneous breathing in stage 3 of MV
	Reasons for failure to sustain stage 3 of MV
	Successful extubation
	Reasons for extubation failure
	Mortality during stage 3 of MV or within 48 hours after extubation
Independent variables	Individualised CPAP programme
Confounding variables	HIV status
	Smoking history
	Admission criteria to ICU according to the Simplified Acute Physiological II Scale (SAPS II).
Demographic variables	Age
	Gender

3.7 STUDY PROCEDURES

Due to the clinical involvement of the researcher in the daily patient care in ICU, an independent research assistant was used to collect the confounding, demographic and dependent variables, as well as the outcome measures used in this study for subjects in both groups. The research assistant was blinded and unaware of the group in which each subject was placed. This arrangement minimised the possibility of bias (Appendix 13: Research Assistant: Letter of appointment).

3.7.1 Instruments

The following instruments were used and developed to test the hypothesis and to answer the research question.

3.7.1.1 Standard procedure

The standard weaning procedure of subjects used in the ICU at Cosmos Hospital was based on the experience and subjective assessment of the attending physician, surgeons, anaesthesiologists and nursing staff. There was no existing standardised weaning protocol or criteria for spontaneous breathing trials or extubation. No objective measurements were used to assess readiness for weaning, SBT or extubation. Subjects were generally weaned (stage 2 of MV) to minimum MV support of a rate of four ventilator breaths/min, pressure support of 10 cmH_2O, a PEEP of 5 cmH_2O and a FiO_2 of 50% or lower. Subjects were then either extubated or placed on CPAP (stage 3) until they could not sustain spontaneous breathing on CPAP and had to go back to stage 1 or 2 of MV. Subjects were extubated when the attending medical practitioner determined subjectively that the subject was able to breathe independently without MV support.

3.7.1.2 Intervention procedure

Based on the evidence found in the literature review section of this dissertation, an evidence based weaning protocol was developed. This was done through a collaborative process among the attending physicians, surgeons, anaesthesiologists, researcher, physiotherapists and nursing staff who worked in the unit and who agreed to the content of the protocol. This weaning protocol used by Grap et al (2003) was modified to include the following three steps:
Step 1: which consisted of: a) daily screening for readiness for SBT with set objective and subjective measurements and observation criteria, (b) calculation of the RSBI [high in specificity and sensitivity (Bittner et al 2009)], (c) measuring the MIP, procedures described below]
Step 2: implementation of SBT protocol with termination criteria

Step 3: implementation of an individualised CPAP program with set termination criteria and daily progression specified, and calculation of RSBI rate to determine the daily progression of the individualised CPAP program (Appendices 3 and 6). The protocol included weaning algorithms that were practical and evidenced based, as described by Esteban (1994) and Ely et al (1996). A weaning protocol flow chart was developed by the researcher and placed at each subject's clinical chart as a visual reminder for the attending staff on the exact procedure to follow (Appendix 7: *Weaning flow chart*).

Step 1: Daily Screening for Readiness for a Spontaneous Breathing Trial

a) **Daily screening for readiness for a spontaneous breathing trial**

A daily screening test for a SBT was developed based on available evidence and recommendations as discussed in the literature review section of this dissertation. (Appendix 3: *Screening Form 1-3*). Screening was performed every morning at 08h00 by the attending nurse and recorded on screen form 1 (Appendix 3: *Screen Form 1*). Subjects had to score positive on all of the following questions before proceeding to the next screen form: 1) haemodynamic stability; 2) PaO_2/FiO_2 ratio > 150 or SaO_2>95% on 50% FiO_2 or less; 3) PEEP set at 5cmH_20; 4) Pressure support of 10 cmH_2O or less; and 5) Richmond agitation-sedation scale (RASS) of -2 or higher [the RASS was developed and validated by Grap et al (2003)]. A negative answer to question two: Off vasopressor? (Adrenaline) did not hinder progress to the next screen form as the leading physician in the ICU concluded that, if all other questions were positive, the subject should be stable enough to proceed to the next screen.

b) **Calculation of Rapid Shallow Breathing Index**

Rapid shallow breathing index protocol:

The RSBI of the subjects who passed the first screening form (Appendix 3: *Screen form 2)*, was calculated immediately after the daily screening by the researcher as described in the literature review section (chapter two point 2.4.1) of this dissertation. The following RSBI protocol used by Grap et al (2003) was used: ventilator respiratory rate was reduced to 0, the PEEP was left on 5cmH_2O, the pressure support was reduced to 0cmH_2O and the trigger flow turned down to zero. The subject was observed for one minute and the spontaneous respiratory rate (RR) and inspiratory tidal volume (Vti) were recorded. The subject was then placed back on the pre–test MV settings. The RSBI was calculated as follows: RSBI = (RR/Vti) x 100 (Tobin & Jubran, 2006) (Appendix 4: *RSBI protocol*) and recorded on the screen form 2 (Appendix 3: *Screen 2).*

If the RSBI was higher than 100b/min/l the subject was left on the pre-screen MV settings and reassessed on screen 1 the next day. Subjects who had a RSBI of below 100b/min/l were progressed to a SBT (Appendix 3: Screen 3: *Spontaneous Breathing Trial*).

c) **Maximum inspiratory pressure measurement protocol**

The protocol for MIP measurement found in the instruction manual of the Vela Ventilators was used in this test setting. (Appendix 5*: Vela Ventilator Systems. Operators Manual: pg. 79 L1533/ Revision E. MIP protocol*). The following steps were taken: a) subject put on CPAP mode with PEEP of 8cmH_2O or below; b) pressure support of 10cmH_2O or below; c) the highest MIP generated during 30 seconds was recorded. The MIP was calculated immedialty after the daily screening and recorded for data collection purposes only (Appendix 3: *Screen 2).* The decision to include the MIP was taken to test the statements made by previous researchers that the MIP test could be unreliable and difficult to perform on subjects who are on MV

Step 2: Spontaneous Breathing Trial

The subjects who passed the RSBI test (<100b/min/l) were placed on a SBT. This was done by the researcher placing the subject onto CPAP on the ventilator, with the flow trigger set on 1, the pressure support on < 8cmH_2O and the PEEP on 5cmH_2O. The following strict termination criteria for the SBT were set: a) RR > 35/min for 5 minutes or more, b) a SaO_2 <90% for five minutes or more, c) a HR >140/min or a sustained increase of 20% above the baseline of that subject for 30 minutes or longer, d) a systolic BP of >180 mmHg or < 90mmHg for 30 minutes or longer, and e) increased anxiety of the subject. The SBT was terminated if a subject demonstrated any of the termination criteria. The time of the SBT before termination and the reason for termination were recorded by the researcher on screen 3 (Appendix 3: Screen 3: *Spontaneous Breathing Trial*). Subjects who displayed none of the termination criteria signs were left on the SBT for a maximum of 120 minutes, and then placed back on the pre-SBT MV settings for two hours, in order to rest, before being progressed to the individualised CPAP programme.

Step 3: Individualised Continuous Positive Airway Pressure Program

Based on the time that the subject was able to stay on the SBT, the researcher determined the individualised CPAP program for each subject. This was documented on the daily CPAP program (Appendix 9: Daily CPAP Programme Schedule).

The individualised CPAP program (Appendix 6: *Individualised CPAP program*) was developed taking cognizance of the following:

i) The physiological properties of respiratory muscles [spontaneous breathing on CPAP will have an effect on the type I slow twitch endurance muscle fibres of the diaphragm, whereas breathing via a T-piece or tracheal mask will affect the type II strength fibres of the diaphragm];

ii) Evidence on the benefits of sub-maximal exercise testing and training (60 - 75% of maximum effort) on type I muscle fibres to prevent low frequency fatigue of the diaphragm. The decision to use 75% of maximum effort was taken due to the strict termination criteria of the protocol;

iii) Specific adaptation to imposed demand (SAID) and overload exercise principles specific to type I muscle fibres, by using the daily adjustable progressive resistive training (DAPRE) method used in muscle strength training as described in the literature review (chapter 2, section 2.7.1.) of this dissertation;

iv) Prevention of low frequency fatigue of the diaphragm by allowing adequate rest and recovery periods after and between each training session. The rest periods were adjusted daily in a descending manner to ensure that the adaptation of the muscle fibres achieved by the increased workload of the ascending CPAP progression did not reach a plateau; and

v) Adaptation of each subject's individualised CPAP program to match their individual capacity, as determined by daily assessment and evaluation of the vital and clinical signs.

The researcher determined the individualised CPAP programme of each subject by calculating 75% of the SBT time to use for the first day's CPAP programme eg. if the subject was able to cope on the SBT for less than 15 minutes; he/she was placed on CPAP for only 10 minutes. After this CPAP period the subject was placed back on the pre-SBT MV settings for 180 minutes to rest. . If the subject was able to remain on the SBT for 15 minutes before termination of the SBT, he/she was placed on the CPAP programme for 10 minutes and rested for 120 minutes. The sequence of CPAP and rest periods was repeated three times during the day. Subjects who were able to stay on a SBT of 30 minutes or longer were placed on 75% of their CPAP time, a rest period of 60- 90 minutes depending on their CPAP time and then placed on a T-piece, connected to the MV, for 75% of the CPAP time. This was done to also recruit type IIa (FT) fibres, in order to improve the strength component of the diaphragm. Pierce (2006) stated that breathing via a T-piece requires higher work force and may recruit type IIa fibres. Consensus was reached among the team that subjects who were able to

sustain a SBT of less that 30 minutes should not be placed on a T-piece in order to minimize the risk of low frequency fatigue of the diaphragm. The individualised CPAP program is displayed in Table 3.1.

Table 3.1: Individualised Continuous Positive Airway Pressure Programme

SBT Time	**CPAP Period:** (75% of SBT time) Individual PEEP and PS settings.	**Rest Period:** Pres-SBT MV Settings	**T-piece Period** (75% of CPAP) period time. Individual PEEP and PS settings.	**Rest Period**	**Repeat Sequence during** day
< 15 min	10 min	180 min	No T-piece	NA	3
15 min	10 min (11.25 min)	120 min	No T-piece	NA	3
30 min	20 min (22.5 min)	90 min	15 min	60 min	3
60 min	45 min	60 min	30 min (33.8 min)	60 min	3
90 min	65 min (67.5 min)	60 min	50 min (48.8 min0	60 min	3
120 min	90 min	60 min	70 min (67.5 min)	60 min	3

It was the duty of the attending nurse to adjust the ventilator of the subjects in accordance with the subject's individualised CPAP programme. Strict criteria for the termination of the individualised CPAP programme were set: a) RR > 35/min for five minutes or more, b) a SaO_2 <90% for five minutes or more, c) a HR >140/min or a sustained increase of 20% above the baseline of that subject for 30 minutes or longer, d) a systolic BP of >180 mmHg or < 90mmHg and e) increased anxiety of the subject. Subjects were closely monitored by the attending nurse and any subject who demonstrated any of the above signs was placed back to pre-SBT MV settings and rested until the following morning and then reassessed for SBT readiness the following morning. The reasons for termination of the individualised CPAP programme were recorded by the attending nurse and reported to the researcher.

The RSBI of all subjects on the individualised CPAP programme was tested twice a day by the researcher, to determine their RSBI rate as described in section 2.4.1. The RSBI rate was calculated by obtaining the difference from the first RSBI ($RSBI_1$) of the day and the second RSBI ($RSBI_2$) of the day, and then divided by the result of the $RSBI_1$, multiplied by 100. (RSBI rate = $[(RSBI_2 - RSBI_1)/RSBI_1] \times 100$. The RSBI rate was used to determine whether the subject was coping on the individualised CPAP programme. A RSBI rate of more than 20% of the previous RSBI, after the subjects had been on the individualised CPAP programme for 12 hours, was taken as an indication of possible low frequency fatigue of the respiratory muscles. Subjects with a RSBI rate of > 20% were rested on pre-SBT MV settings during the night.

Subjects with a RSBI rate of < 20% were continued on the individualised CPAP programme during the night.

The RSBI rate of all subjects was calculated, by the researcher, every morning to determine the daily progression of the individualised CPAP programme. Subjects with a RSBI rate of >20%, without showing any of the termination criteria signs for the individualised CPAP programme, were left on the previous day's CPAP programme and only progressed if the RSBI rate was below 20%. This was taken as an indication of adequate rest and no significant fatigue of the diaphragm.

Daily progression of the individualised CPAP was performed according to the daily adjustable progressive training method. The CPAP program for subjects with a RSBI rate of < 20% was as follows: The CPAP time was increased by 50%, the rest periods was decreased by 25% and the T-piece time, if any, was increased by 20%. Subjects with a RSBI rate of >20% remained on on the current day's program, and only progressed the next day if the RSBI rate was <20% of the previous day's RSBI. The researcher determined the daily CPAP programme for each subject and recorded it on the individualised CPAP schedule (Appendix 9: Daily CPAP Programme Schedule), attached to each subject's clinical record. This enabled the day and night staff to follow the programme easily.

The subject's progress on the CPAP programme was reported to the attending physician on the daily ward round. The attending physician made the final decision to extubate or liberate the subjects from the ventilator, based on the subject's progress on the programme and his/her clinical signs and symptoms.

3.8 DATA COLLECTION PROCEDURE

Group One

The researcher monitored admission into the ICU on a daily basis. From 1 December 2008, all patients matching the inclusion criteria were recruited to group one. This group of subjects received the standard weaning procedure as described in section 3.7.1.1, which was in use in the ICU at the time of the study. Informed consent to include the data of the subjects in group one was obtained by the staff [according to the hierarchy prescribed by the Health Professions Council of South Africa (HPCSA)] from the subject, spouse, parent, oldest sibling or hospital superintendent/manager. Information sheets (Appendix 8: *Patient Information Sheet)* on the study procedure were provided to the subjects and/or family members. A member of the nursing staff explained the procedures to the family members, in their own native language, if they could not understand English. The subject and/or family members were given the

opportunity to pose questions to the researcher about the study procedures, if needed. Each subject was allocated a study number from A1 to A24; their personal data was encrypted and stored electronically. The information was password protected, with the password known only to the researcher.

Interval Period

Consensus on the individualised CPAP protocol was obtained from the referring doctors, ICU unit manager and physiotherapists prior to implementation of the protocol for group two.

Once final adjustments to the individualised CPAP protocol had been done and the recruitment of the 24 subjects for group one was completed, the implementation date of the intervention (individualised CPAP protocol) for group two was set for 1 July 2009. There was an interval period of two weeks after the last subject in group one was extubated prior to the date for implementation of the individualised CPAP protocol for group two, in order to allow time for staff training and enable the staff to familiarise themselves with the protocol. Two patients were admitted into the unit during this week and placed on MV. One was extubated within 48 hours and the other was screened for SBT readiness, but did not meet the criteria for a SBT. This subject died after 4 days of MV without ever entering stage 3 of MV.

Extensive education to the unit's multidisciplinary team members, including the nurses, physiotherapists and physicians, was provided by the researcher prior to the implementation of the individualised CPAP protocol.

The following information was included in the training sessions: (a) basic physiology of respiratory muscles; (b) complications of MV on the respiratory system; (c) evidence for the use of systematic MV weaning protocols driven by non-physicians; (d) the roles and importance of the nursing staff and physiotherapists in the protocol; (e) the screening test for SBT readiness; (f) the test procedures for RSBI and MIP; (g) the SBT; (h) termination criteria for the SBT; (i) the individualised CPAP programme; (j) termination criteria for the individualised CPAP programme; (k) daily progression of the individualised CPAP programme until termination of MV, and (l) aim and objectives for the study.

The education sessions were done on four different days to accommodate all shifts of nursing staff, continuous training was given as the need arose. Individual information sessions were held with the physicians and other attending medical practitioners. A weaning protocol flow chart was developed and placed at each ventilator and at strategic places in the unit; this was done as a constant visual reminder of the protocol (Appendix 7: *Weaning Flow Chart*). The education of all staff was done only after the recruitment of all 24 subjects in group one was

completed. This was done to prevent possible spill over from the intervention program to the control group (group one).

Group Two

All subjects admitted from 1 July 2009 who met the inclusion criteria were recruited to group two. Each subject received a study number from B1 to B24; their personal data was encrypted and stored electronically by the research assistant. The information was password protected, with the password known only by the researcher.

Informed consent to include the subjects into the study in group two obtained by the staff, as described in section 3.8 above. The subject and/or family members were given the opportunity to pose questions to the researcher about the study procedures. A member of the nursing staff explained the procedures to the family members, in their own native language, if they could not understand English.

On receipt of consent, the intervention programme was implemented as described in section 3.7.1.2. The following data was captured for both groups in order to measure protocol outcomes in a systematic fashion by the research assistant on site *(Appendix 10: Data capture sheets A and B)*

- Reasons for admission to ICU were categorised as follows: 1 = medical intervention, 2 = elective surgical intervention, 3 = emergency surgical intervention. The Simplified Acute Physiological II Scale (SAP II) was used (Le Gall, Lemeshow and Saulnier 1996).
- Numeric age
- Gender as follows: 0 = male and 1 = female.
- HIV status. The status was classified as follows: 1 = positive, 2 = negative and 3 = unknown. The HIV status was only classified as positive if there was a positive diagnosis of HIV i.e. subjects on anti-retroviral (ARV) drugs or a positive enzyme-linked immunosorbent assay (ELISA) test. The HIV status was classified as negative when the ELISA was negative. Neither the family members nor the subject were ever asked about the subject's HIV status. If the status was unavailable to the research assistant the status was classified as unknown.
- Smoking history. Where possible the subject or family members were asked about the subject's smoking habits and recorded as 1 = positive, 2 = negative and 3 = unknown.
- Number of hours spent in stage 3 (spontaneous breathing stage) of MV was measured from the first hour that the subject was put on CPAP (for group one), a SBT or individualised CPAP (for group two) until the hour of extubation, or failure of the subject to sustain

spontaneous breathing. If a subject failed this stage the additional hours, (measured in minutes and rounded off to hours. Zero to 30 minutes rounded off to zero hours and 30 minutes and more rounded up to one hour) spent on the additional attempts of spontaneous breathing were added to his/her total hours spent in this stage.

- Number of failed attempts of stage 3 of each subject where 0 indicated no failure, 1 indicated one failed attempt and so on.
- Reason for termination of stage 3. This was recorded as 0 = no failure, 1 = subject not coping, 2 = protocol not followed, 3 = developed additional medical condition and 4 = subject taken to theatre.
- Time that the subject spent in stage 1 (full MV support) of MV from the first hour of MV until the first attempt at decreasing/weaning MV support. Support could be decreased or weaned by decreasing the FiO_2, the pressure support, PEEP or breathing support rate. Any failure of any stage where the subject had to be put back onto stage 1 of MV was added to the total number of hours that the subject spent in stage 1. The reasons for failure of stage 1 were not recorded as this was not in the scope of the research study.
- Total hours that the subject spent in stage 2 (weaning stage) from the first hour that MV support was decreased or weaned until the first hour that the subject was put on a SBT or CPAP. Failure of stage 3 where the subject had to be put back to stage 2 was added to the total number of hours that the subject spent in stage 2. Reasons for failure of stage 2 were not recorded as this was not in the scope of the research study.
- Extubation success. Extubation was deemed successful if a subject managed to be free of MV for 48 hours after extubation without the need for reintubation and/or non-invasive MV. Zero indicated successful extubation and one indicated unsuccessful extubation.
- Reasons for extubation failure. These were as follows: 1 = reintubation within 48 hours due to respiratory failure, 2 = subject died within 48 hours of extubation or during stage 3 of MV, 3 = emergency or elective surgery within 48 hours of extubation with a need for reintubation and 4= subject transferred to another facility while still in stage 3 of MV.
- Total number of days that the subject spent on invasive or non invasive MV from the first 24 hours on MV until extubation, termination of MV or death of the subject while on MV.
- Total number of days that the subject spent in ICU from the first 24 hours that the subject was admitted into ICU until discharge from ICU or death of the subject while in ICU.
- Mortality. This was recorded as follows: zero indicated that the subject was alive and one that the subject died during or after stage 3 of MV. The reasons for mortally was not recorded as this was outside the scope of this study.

3.9 ETHICAL CONSIDERATIONS

Ethical clearance for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand on 26/09/2008 nr M080952: (Appendix 11).

Permission from the ICU Steering Committee and Management of Cosmos Life Health Hospital was obtained in September 2008 (Appendix 12).

Permission was obtained from the management of Cosmos Life Health Hospital to collect the data on site (Appendix 12).

Written informed consent was obtained from the subjects and/or family members of subjects according to the hierarchy as described in the Health Professionals Act of 1974 (Appendix 14: *Informed Consent Form*).

Subjects were allowed to withdraw from the study at any time without compromise of standard nursing and medical care.

Confidentiality and privacy of all subjects was maintained by coding all data that was captured on the outcome measurement sheets and the database on the computer of the researcher. Data were stored in a password protected folder on the researcher's computer.

3.10 APPROACHES TO DATA ANALYSIS

At the end of the data collection period, raw data were uploaded into a Microsoft Excel datasheet to allow for initial ordering and capturing of the data. These data files were set into the statistical package "STATA version 10" for Windows and verified by the statistician from the South African Medical Research Council.

Descriptive statistics were used to characterise the sample used in terms of demographic variables (age and gender) and for confounding variables (reasons for admission into ICU, HIV status and smoking history).

Descriptive statistics and frequency distributions were used to analyse the primary outcome variables (hours spent in stages 2 and 3 of MV, total MV days, failed attempts to sustain spontaneous breathing in stage 3 of MV, successful extubation and mortality). Kaplan Meier survival analysis was computed for the hours spent in stages 2 and 3 of MV. Distribution

statistical analysis (frequency) was computed for the reasons subjects failed stage 3 of MV, as well as the reasons for failed extubation.

Statistical tests included the Kruskal Wallis test, Chi-square test, two sample t-test, Kaplan Meier survival curves, the log-rank test and Cox regression analysis. Due to the relatively small sample size of n = 48 (n = 24 per group), the Fisher Exact test was chosen to analyse contingency tables.

Descriptive, comparative and inferential statistics were used to describe and analyse the results from the study to meet the study objectives. Frequency (f), percentages (%), range, geometric mean, 95% confidence intervals CI and standard deviations (SD) were used where applicable to describe the data. Testing was done at the 5% ($p<0.05$) level of significance and ensured a power of at least 90% accuracy in findings.

The results and analysis of the data collected during this study will be presented in Chapter 4.

CHAPTER 4

4. RESULTS

This chapter describes the results obtained from the prospective non-randomised experimental study that was described in the previous chapter. Graphs and tables are used to present the study results for easier interpretation and understanding of the study outcomes. Percentages are rounded off to one decimal point.

4.1 DEMOGRAPHIC INFORMATION AND CONFOUNDING VARIABLES

Descriptive statistics are used to characterise the sample used in terms of demographic variables (age and gender) and for confounding variables (SAPS II admission criteria, HIV status and smoking history).

Table 4.1 illustrates the combined demographic and confounding variable distribution displayed by group. Since the intervention and control groups do not differ significantly with respect to demographic or confounding variables, further testing conducted did not control for these. It can therefore be accepted that the two groups are well matched with respect to the demographic and confounding variables.

Table 4.1: Comparison of Combined Demographic and /Confounding Variables for each Group (frequency (%).

Variable	Categories	Entire sample: (n = 48)	Group one: Control (n=24)	Group two: Intervention (n=24)	p-Value
Gender	Male	37 (77.1%)	19 (79.2 %)	18 (75.0 %)	1.00
	Female	11 (22.9%)	5 (20.8 %)	6 (25.0 %)	
Smoking*	Yes	18 (37.5%)	10 (50.0 %)	8 (57.1 %)	0.74
	No	16 (33.3%)	10 (50.0 %)	6 (42.9 %)	
HIV*	Yes	16 (33.3%)	10 (58.8%)	6 (46.2%)	0.71
	No	14 (29.2%)	7 (41.2%)	7 (53.8%)	
SAPS II	Medical	29 (60.4%)	13 (54.2 %)	16 (66.7 %)	0.89
	Elective surgery	8 (16.7%)	5 (20.8 %)	3 (12.5 %)	
	Emergency surgery	11 (22.9%)	6 (25.0 %)	5 (20.8%)	
Age**		**Entire Sample:** (n=48)	**Group one: Control** (n=24)	**Group two: Intervention** (n=24)	**p-Value**
	Mean (SD)	38.7 (±8.77)	37.3 (±8.29)	40.1 (±9.19)	0.28
	95% CI	(36.2 ; 41.3)	(33.8 ; 40.8)	(36.2 ; 44.0)	

HIV – human immunodeficiency virus; SAPS II – Simplified Acute Physiological II Scale.

*Smoking and HIV status was not known for all subjects. The p-values were adjusted for HIV and smoking status by deleting the unknown groups.

** Results expressed as geometric mean (± SD) and 95% CI.

4.2 PRIMARY OUTCOMES

Descriptive statistics are used to analyse the primary outcome variables (hours spent in stage 2 and 3 of MV, total MV days, failure to sustain stage 3 of MV, success rate of extubation and the mortality rate during stage 3 or within 48 hours of extubation) per group.

4.2.1 Time Spent in the Different Stages of Mechanical Ventilation

Table 4.2 illustrates the combined results for the primary outcome variables per group, namely time spent in the different stages of MV [stage 2 (weaning stage), stage 3 (spontaneous breathing stage)] and the total number of days on MV. The p-value was computed using the student's t-test for time in the different stages of MV.

There are no statistically significant differences between the groups, in relation to the time spent in stage 2 of MV or in the total time spent on MV, but there is a statistically significant difference between the groups (p = 0.01) in the time spent in stage 3 of MV. Subjects in the intervention group stayed longer in stage 3 of MV than those in the control group. A mean of 48.5 hours was spent in stage 3 of MV by the intervention group compared to a mean of 19.2 hours by the control group.

Table 4.2: Comparison of Groups with Respect to Time Variables (expressed in geometric mean, 95% confidence intervals and p-value).

Time Variable	Group One: Control (n= 24)	Group Two: Intervention (n=24)	Students t-test for log transformed time p-Value
Stage 2 of MV (Hours)	157.5 (0.42 ; 283.1)	148.6 (100.8 ; 219.0)	0.83
Stage 3 of MV (Hours)	19.2 (10.3 ; 36.1)	48.5 (32.7 ; 71.5)	0.01
Total MV Days (Days)	13.0 (5.8 ; 12.8)	9.3 (6.8 ; 13.7)	0.75

MV – mechanical ventilation;

Kaplan-Meier survival analysis was computed for the hours spent in stage 3 and also stages 2 plus 3 of MV where the event of interest was failure to liberate from MV (see figures 4.1 and 4.2). This was done to determine if the time that subjects in each group spent in the different stages of MV made a difference in the number of failed extubation events. The stay curves are compared with the log rank test. The Kaplan-Meier curves for stay in stage 3 of MV do not differ significantly between groups (p = 0.5). The Kaplan–Meier curves for time spent in stages 2 plus 3 of MV for both groups also do not differ significantly (p = 0.73).

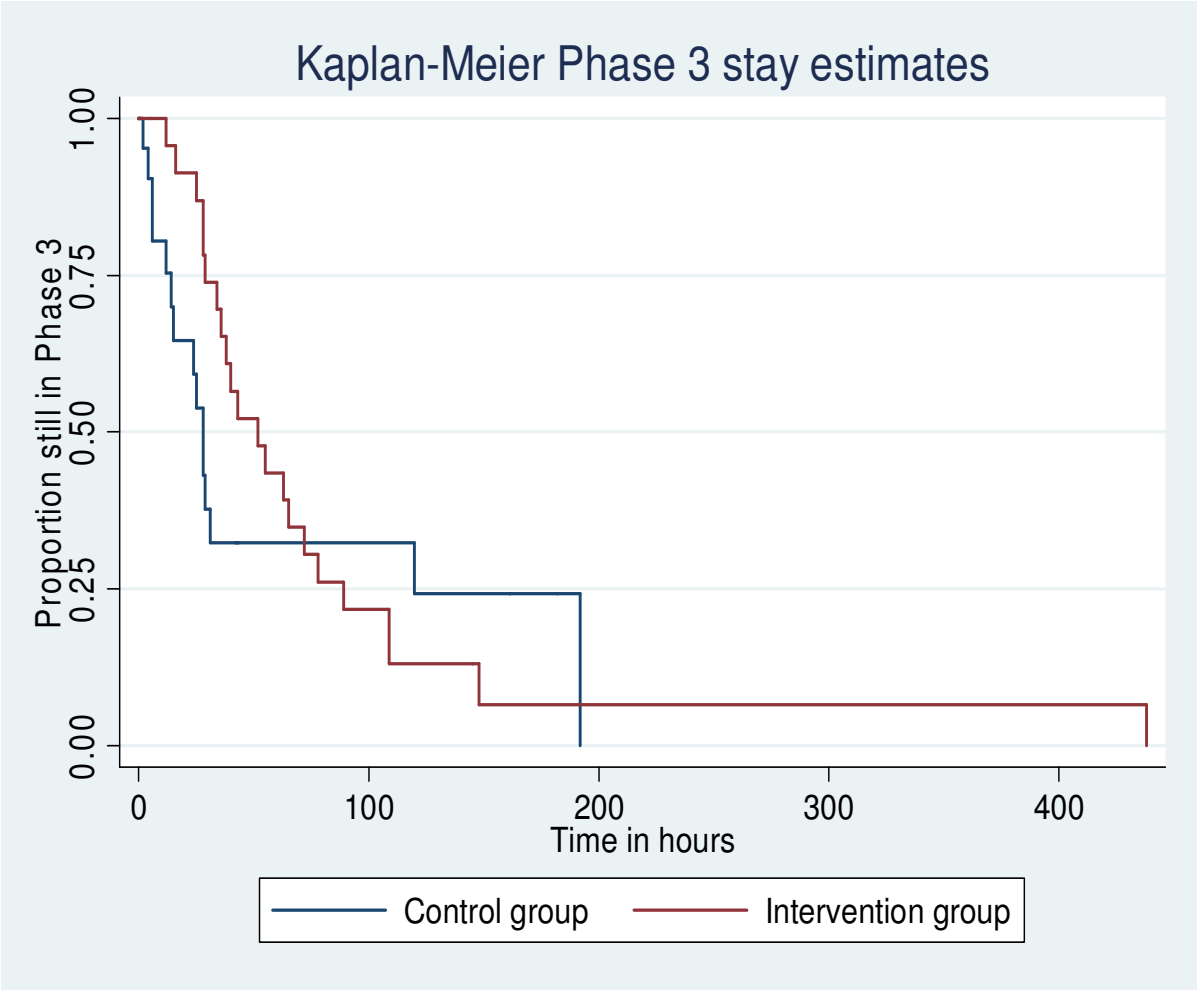


Figure 4.1: Kaplan-Meier Curves for Time in Stage 3 of Mechanical Ventilation where the Event of Interest was Extubation Failure

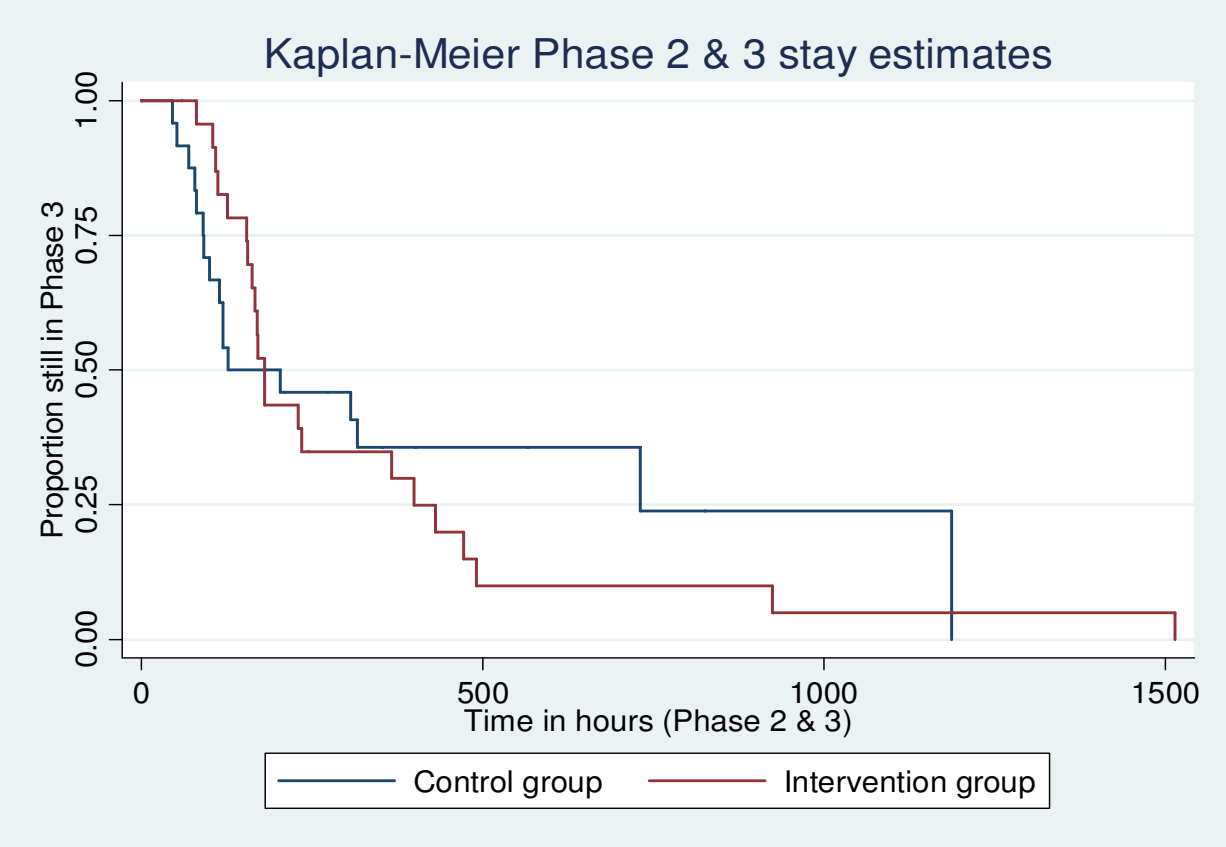


Figure 4.2: Kaplan-Meier Curves for Time in Stage Two plus Stage Three of Mechanical Ventilation Where the Event of Interest was Extubation Failure

4.2.2 Failure to Sustain Spontaneous Breathing in Stage Three of Mechanical Ventilation, Success Rate of Extubation and the Mortality Rate within 48 Hours of Extubation

Descriptive statistics, log rank and Cox regression data for the primary outcomes of failure to sustain spontaneous breathing in stage 3 of MV (failed stage 3), successful extubation and the mortality rate 48 hours after extubation are displayed in table 4.3. There is a statistically significant difference for failed stage 3 events as well as mortality rate between the two groups.

Table 4.3: Comparison of Groups with Respect to Failed Stage Three of Mechanical Ventilation, Successful Extubation and Mortality During or After Stage Two of Mechanical Ventilation (expressed in frequency (%), p-Value, hazard ratio and 95% CI).

Outcome Variable	Entire Sample: (n = 48)	Group one: Control (n=24)	Group two: Intervention (n=24)	Log-rank test p-Value	Cox regression * p- Value	Hazard Ratio (95% CI)
Failed stage 3 of MV	13 (27.1%)	10 (41.7%)	3 (12.5%)	0.01	0.02	0.16 (0.03 ; 0.73)
Successful extubation	39 (81%)	17 (70.8%)	22 (91.7%)	0.52	0.53	0.80 (0.41 ; 1.58)
Mortality rate during or after stage 3 of MV	10 (20.8%)	8 (33.3%)	2 (8.3%)	0.02	0.03	0.18 (0.04 ; 0.85)

MV – mechanical ventilation

* From uni-variant analysis it followed that no co-variants had to be controlled for in the Cox regression comparing study groups. The most likely co-variant to adjust for would have been the time spent in stage 2 of MV. However, when controlling for time in stage 2 of MV, the hazard ratio per group, when considering time spent in stage 3 of MV, was unchanged.

The Cox regression analysis (p = 0.02) undertaken to ascertain the rate of failure to sustain spontaneous breathing in stage 3 of MV is statistically significant. The Hazard Rate of 0.16 and a CI of (0.03 ; 0.73) shows that only 16% of the subjects in the intervention group were prone to failure in this stage of MV as a result of the intervention; this means that 84% of the subjects in the intervention are protected against failure to sustain spontaneous breathing in stage 3 of MV due to the implementation of the individualised CPAP programme.

The Cox regression for successful extubation is not statistically significant (p = 0.53) but the Hazard Rate of 0.80 with a 95% CI of (0.41 ; 1.58) shows that in 80% of extubation attempts the intervention (individualised CPAP programme) protected the subjects against extubation failure.

4.2.3 Reasons for Failure of Stage Three of Mechanical Ventilation and for Extubation Failure

Descriptive statistical analysis is used to characterise the reasons for failure of stage 3 and for extubation failure. These results are displayed in Tables 4.4, 4.5 and 4.6.

Table 4.4: Number of Failed Spontaneous Breathing and Extubation Events in Stage Three by Group (frequency (%).

	Number of failed attempts to sustain spontaneous breathing in stage 3 of MV	Number of failed extubation events
Group One: Control (n=24)	10 (41.7%)	7 (29.2%)
Group Two: Intervention (n=24)	3 (12.5%)	2 (8.3%)
Entire sample (n=48)	13 (27%)	9 (18.8%)

MV – mechanical ventilation

Table 4.5: Reasons for Failed Spontaneous Breathing in Stage Three by Group (frequency (%).

	Reasons for failure of stage 3 of MV (% of failure per group)		
	Subject not coping on stage 3 of MV, met one of termination criteria, was put back to stage 2 of MV	Subject developed additional medical complication, was put back to stage 2 of MV	Subject underwent elective/emergency surgery, was put back to stage 2 of MV
Group One: Control (n=10)	8 (80%)	2 (20%)	0 (0%)
Group Two: Intervention (n=3)	3 (100.3%)	0 (0%)	0 (%)
Entire sample (n=13)	11 (84.5%)	2 (15.4%)	0 (0%)

MV – mechanical ventilation

Table 4.6: Reasons for Failed Extubation by Group (frequency (%).

	Reasons for extubation failure (% of failure per group)			
	Respiratory failure within 48 hours of extubation	Subject died within 48 hours from extubation or during stage 3 of MV	Emergency/elective surgery within 48 hours of extubation need for reintubation	Transferred to other facility still ventilated and in stage 3 of MV
Group One: Control (n=7)	5 (71.4%)	0 (0%)	2 (28.6%)	0 (0%)
Group Two: Intervention (n=2)	0 (0%)	1 (50%)	0 (0%)	1 (50%)
Entire sample (n=9)	5 (55.6%)	1 (11.1%)	2 (22.2%)	1 (11.1%)

MV – mechanical ventilation

There were 10 events of failure to sustain spontaneous breathing in stage 3 of MV in the control group and only three events in the intervention group. Eight of these events in the control group were due to the subjects showing signs of distress (according to the subjective observation of the attending staff) and two events were due to the subjects developing additional medical complications necessitating being put back into stage 2 of MV. There were three failed events during stage 3 of MV in the intervention group; one where the attending nurse left the subject too long on CPAP (continuous for 12 hours) during the night. This subject showed signs of distress (hyperventilation above 35 b/min for more than 30 minutes) during this period, but this was overlooked by the attending nurse. The RSBI and RSBI rate of this subject were tested the following morning and because of a deterioration of the RSBI (above 100 b/min/l) and a RSBI rate of more than 20% of the previous day's RSBI, it was decided to put the patient back to stage two of MV until his RSBI was below 100b/min/ ℓ. Subsequently, this subject was rested on a comfortable mode of ventilation for 48 hours as advocated by MacIntyre et al (2007), retested for SBT readiness and the individualised CPAP programme reinstituted with positive outcomes. The other two subjects developed signs of distress in the intervention group but passed another SBT after 24 hours of rest on MV support and were put back on the individualised CPAP programme.

Seven events of failed extubation were reported in the control group. Five subjects failed extubation and had to be reintubated within 48 hours due to respiratory arrest; the remaining two events were due to the subjects undergoing elective or emergency surgery within 48 hours after extubation which lead to reintubation and mechanical ventilation. The last two events were not under the control of the researchers and should not have been reported as extubation failure. Two failed extubation events were reported in the intervention group; one subject developed cardiac arrest within 48 hours after extubation and subsequently died and one subject was transferred to another facility while on CPAP due to medical aid issues outside of the control of the researchers. This last event should not have been reported as extubation failure, as the outcome of this subject's extubation was not known.

4.3 Rapid Shallow Breathing Index Distribution for Group Two

The first RSBI, taken during the screening test for SBT, for group two is displayed in Figure 4.3. Only one (4.2%) of 24 subjects in group two had a RSBI of above 100 b/min/ℓ (>100b/min/ℓ was considered as a good predictor of weaning success).

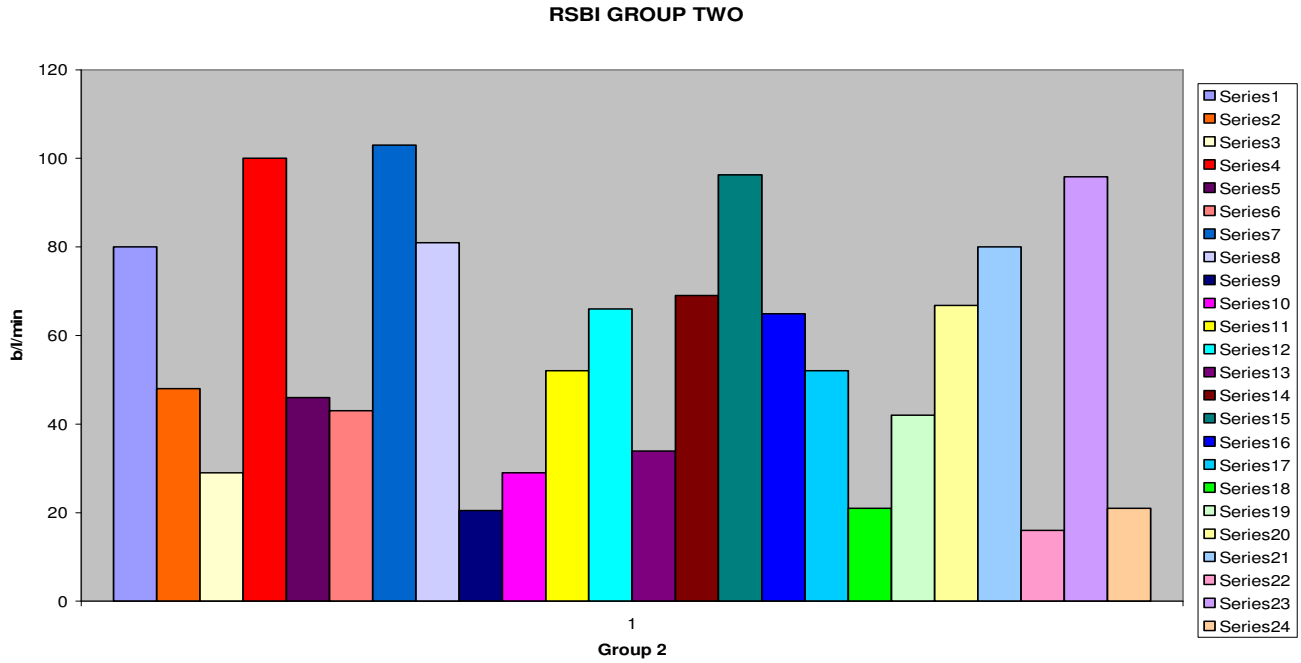


Figure 4.3: Rapid Shallow Breathing Index Distribution for Group Two

RSBI - Rapid Shallow Breathing Index: B/L/MIN - breaths per minute per litre; B1 – B24; - study number of subjects in group two

4.4 Maximum Inspiratory Pressure for Group Two

Eleven of the 24 subjects (45.8%) in group two had a MIP of below the accepted indicator of sufficient respiratory strength of -20cmH_2O, on their first screening test for SBT readiness. The

mean was - 21.75cmH_2O (SD - 6 to -40 cmH_2O). All eleven subjects were all able to continue to a SBT.

Figure 4.4 reflects the first MIP measurements taken for group two.

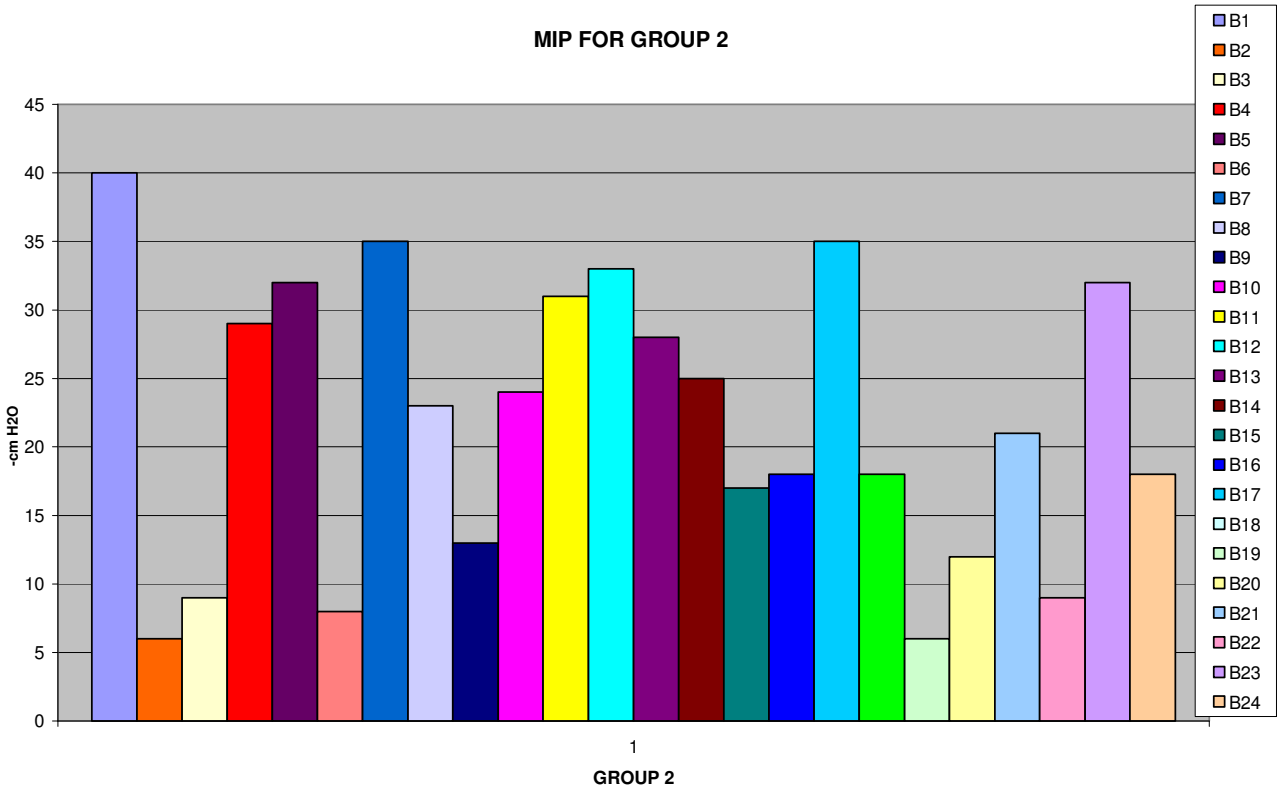


Figure 4.6: First Maximum Inspiratory Pressure Measurements for Group Two

MIP - Maximum inspiratory pressure; B1 – B24,- study number of each subject in group two

4.5 Summary of Statistical Results

The demographic and confounding variables shows no significant differences between the study groups and it could therefore be assumed that the two groups are well matched. There are no statistically significant differences in the time that the subjects spent in stage 2 of MV (weaning stage) ($p = 0.83$) or in the total MV time ($p = 0.75$), but there is a statistical difference in the time spent in stage 3 of MV (spontaneous breathing stage) ($p = 0.01$). The Kaplan-Meier survival curves for time in stage 3 ($p = 0.5$) and stages 2plus 3 ($p = 0.73$) where the event of interest was failed extubation, shows no statistically significant differences between the two groups.

The log rank test shows a statistically significant difference ($p = 0.01$) between the two groups, with respect to subjects failing to sustain spontaneous breathing in stage 3 of MV as there were 12 failed events in group one and only three in group two. The Cox regression analysis

shows a significant difference between groups ($p = 0.02$) for the failed spontaneous breathing events and a hazard ration of 0.16; this indicated that there was a 16% chance that subjects in group two would have a failed spontaneous breathing attempt compared to 74% in group one.

The data collected for the RSBI [only one of 24 subjects (4.2%) in group two had a RSBI above 100b/min/l] indicates that this could be an objective indicator of readiness for a SBT. The opposite could be said for the data collected for the initial MIP. Eleven of the 24 subjects (45.8%) had a MIP of below -20cmH_2O, but were able to continue on a SBT; this can be an indication that this test is not a reliable objective measurement of respiratory muscle strength to sustain independent breathing in this particular study population. Our findings regarding the clinical significance of MIP support those ideas expressed by other authors (Caruso, Carnieli, Kagohara, Anciaes, Segarra and Deheinzelin 2008).

In chapter 5 the results of this study will be discussed in depth and comparisons to results reported by other researchers will be made. Limitations of this study will be highlighted and further research recommendations will be made.

CHAPTER 5

5. DISCUSSION

This study tested the implementation of an individualised CPAP programme during the spontaneous breathing stage of a weaning protocol, to determine whether it would lead to an improvement in the outcomes of extubation of adult subjects on MV in the ICU. General objectives of this study were to establish whether the use of an individualised graded CPAP programme during the spontaneous breathing stage of a weaning protocol would be more effective in improving weaning outcomes for subjects on MV than a standard weaning protocol.

Specific objectives of this study were: a) to determine the availability of a set of non-invasive, easy-to-use and readily available clinical screening tools to be used as indicators to evaluate the strength and endurance of the respiratory muscles of adult subjects who were mechanically ventilated; b) to determine the availability and clinical appropriateness of a test that could predict the duration that a subject could sustain spontaneous breathing episodes before task failure; c) to develop and implement a CPAP programme, utilising basic muscle rehabilitation principles, which could be individualised for each adult subject who was mechanically ventilated and d) to measure the effectiveness of the individualised CPAP programme in the third stage of MV (spontaneous breathing stage) on the outcomes of adult subjects who were mechanically ventilated. Information obtained from the literature review revealed that a number of non-invasive, easy-to-use clinical screening tools exist to evaluate a subject's readiness for commencement of weaning; however many of these screening tools reportedly had high sensitivity but low specificity and where not recommended for use in a clinical setting; therefore objective (a) could not be met. The MIP, RSBI and RSBI rate were reported to have good sensitivity for use in a clinical setting to determine a subject's ability to sustain spontaneous breathing and were used in the current study; however our results showed that MIP was not specific in determining respiratory muscle strength and therefore objective (b) was partially met. Objectives (c) and (d) were met and will be discussed further and will be compared to findings reported by other authors.

Despite the fact that this was a prospective, non-randomised, sequential study, the demographic information such as age and gender was well matched within the control and intervention groups. The confounding factors such as HIV status, smoking history and admission criteria were also well matched within the two groups. Subjects and/or family members, where possible, were only asked about current smoking history and not about past history. The smoking status of 14 out of 48 subjects was unknown; the research assistant was

for various reasons, unable to follow this up. This unknown factor could have altered the p-value of the comparison of the two groups with regard to the smoking status. Analysis of the confounding factors, as listed above, on the outcomes of extubation was not within the scope of this study, but could be a valuable addition to future studies.

The time that the subjects in the current study spent in the 1st stage of MV was not taken into consideration during data collection and analysis due to the fact that there was many factors outside the control and scope of this study that could have affected the time that subjects spent in stage one of MV. This is also true for the total time that the subjects spent in ICU.

The mean time that the subjects in each group spent in stage 2 of MV did not differ statistically but could however be of clinical significance. Subjects in the intervention group spent 8.9 hours less in stage 2 of MV compared to the control group. This could be due to the implementation of the screening test to determine readiness for a SBT. Subjects in the intervention group were thus placed on a SBT sooner and were carefully monitored for any signs of low frequency fatigue and distress by calculating their RSBI and RSBI rate on regular intervals while on the individualised CPAP programme.

Subjects in the intervention group spent on average 29.3 hours in stage 3 of MV, without this having a significant impact on the overall time spent on MV between the two groups. No studies were found in the literature review to use as comparison with our results relating to time spent in the different stages of MV due to the fact that the stages of MV of the current study were different to that described in the literature (as discussed in chapter one of this dissertation).

Several authors reported a decrease in failed weaning attempts and improved extubation rates by the introduction of earlier spontaneous breathing attempts (Stawicki 2007; Putensen et al 2006; Robertson 2003; Ely et al 2001). This was also evident in the findings of this study.

The inclusion criteria for this study determined that all of the subjects be on MV more than 48 hours. All of the subjects that failed the spontaneous breathing stage of MV (13 events for the entire study group) were ventilated for longer than 48 hours. Although not tested, it may be possible that they had signs of structural abnormality of the respiratory muscle fibres, such as atrophy and muscle fibre remodelling, as reported in multiple studies (Callahan et al 2008; Levine et al 2008; Vassilakopoulos and Petrof 2004; Powers et al 2002; Sassoon 2002; Shanely et al 2002; Yang et al 2002; and Talmadge 2000) after prolonged MV, with

subsequent reduced respiratory muscle weakness and reduced inspiratory muscle endurance (Chang et al 2005). This may have resulted in the inability to sustain spontaneous breathing.
Low frequency fatigue of the respiratory muscles is also suspected in subjects in the intervention group who failed the spontaneous breathing stage due to the fact that they all passed a SBT after a 24 hour rest period on MV support. This correlates with the findings of various authors that low frequency fatigue of the respiratory muscles recovers 24 hours after the cessation of strenuous muscle activity (Polkey and Moxham 2001; Supinski, Fitting and Bellemare 2001; Laghi, D' Alfonso and Tobin 1995; and Aubier et al 1981).

The extubation success rate for the control group was 70.8%, which is lower than the findings reported by Stawicki (2007) who stated that a success rate of between 90-95% is desirable. The success rate for the intervention group was 91.7%, and although the difference between the groups was not statistically significant, it correlates favourably with the desired extubation success rate of 90-95% advocated by Stawicki (2007). The extubation rate of the intervention group in this study is much higher than reported by several other authors. Ambrosino (2005), Grap et al (2003), Ely et al (2001) and MacIntyre et al (2001) reported success rates of only 60–80%. All of these authors advocated permanent withdrawal of ventilatory support if the patient could tolerate a SBT of two hours. The current study differed from the above by introducing an individualised CPAP programme following a successful SBT. The individualised CPAP programme was based on the principles of muscle rehabilitation as well as recommendation 12 of the American Association of Respiratory Care, as discussed in the literature review and the methodology chapters of this dissertation.
Tobin et al (2006, 2002) as well as Meade et al (2001) stated that a RSBI value of below 100 b/min/ℓ is a reliable predictor of readiness for a SBT that could easily be performed in ICU. Although the sensitivity and specificity of the RSBI was not tested in this study it was an easy and quick objective measurement of readiness for a SBT. The RSBI of 23 of 24 subjects (95.8%) in the intervention group was below 100b/min/ℓ. One subject had a RSBI of 105b/min/ℓ but due to his overall excellent status the researcher decided to continue this subject onto the SBT and the individualised CPAP programme with favorable results. Stawicki (2007) and Steiner et al (2006) both reported that a RSBI rate of above 20% of the previous RSBI was a reliable indicator of low frequency fatigue. The first RSBI rate of 17 subjects (n=24) (70.8%) in the intervention group was within the parameters reported in the aforementioned studies. The RSBI rate was calculated, as described in chapter 3.7.1.2 of this dissertation, for all subjects in the intervention group (Group two) after 24 hours on the individualised CPAP programme and subsequently twice a day. The daily RSBI rates provided the researcher with an objective measurement to determine if subjects in the intervention group were coping with the daily

progression of the CPAP program (increased CPAP time and decreased rest periods). Testing the RSBI and RSBI rate for sensitivity and specificity was not in the scope of this study.

Tobin, Brochard and Rossin (2001) stated that the measurement of MIP in the clinical setting can be used to assess inspiratory muscle strength. The manoeuvre that Tobin, Brochard and Rossin (2001) described consists of a maximum inspiratory effort against a closed airway and requires a considerable degree of patient cooperation and coordination. The patient is asked to perform maximum inspiratory efforts for 15-20 seconds and the highest MIP generated during this period is recorded (Tobin, Brochard and Rossin 2001). This was similar to the MIP testing protocol used in the current study. As early as 1994, Moxham and Goldstone reported that the measurement of respiratory muscle strength in the ICU could be difficult and inaccurate because it is difficult to ensure a maximal effort from the patient. The reliability of the MIP test, used in the current study, can be questioned as the daily MIP values of subjects in the intervention group changed according to their level of consciousness and understanding of the procedure. This correlated with the statement made by Caruso et al (2008) and Callahan (2008) that sedation, mode of ventilation, lack of motivation and glucose control could affect the evolution of daily MIP measurements during MV. In 1999 Caruso et al stated that the use of a unidirectional valve allows MIP to be performed easily in uncooperative patients. This method should be incorporated in weaning protocols, as part of the screening for SBT readiness, in the average clinical ICU setting. According to Tobin, Brochard and Rossin (2001) a MIP of above -20 cmH_2O is an indicator of adequate respiratory muscle strength to sustain independent breathing. The mean MIP of - 21.75 mH_2O in the intervention group of the current study could indicate decreased inspiratory muscle strength as stated by Tobin, Brochard and Rossin (2001), however all eleven subjects that had low MIP's had acceptable RSBI and RSBI rate results. They were all able to continue onto a SBT, as well as the individualised CPAP program, with good outcomes, despite the low MIP. It can therefore be concluded that the use of MIP alone, was not a useful objective test of readiness for a SBT or, by implication, of inspiratory muscle strength. MIP together with the RSBI was a better test for readiness for a SBT. The addition of the RSBI rate was a good indication that the subject was coping on the individualises CPAP program,

The mortality rate in the current study was higher in the control group than the intervention group. The mortality rate for the control group compares with the 34-35% mortality rate reported in a multi-centre study done in the USA by Zilerberg et al in 2008. Ambrosino (2005) and Zwillich, David, Creaqh, Sutton, Schatz and Petty (1974) stated that the complications of MV such as ventilator induced diaphragmatic dysfunction and low frequency fatigue could

increase morbidity and mortality up to 30%. Tobin (2002) stated that each failed extubation increased mortality rate by 20%. It would be reasonable to assume that the implementation of the individualised CPAP programme may have had a positive effect on the decreased mortality rate seen in the intervention group. It could be speculated that the increased extubation rate and decreased failed spontaneous breathing attempts reported for the intervention group might have played a positive role in the decreased mortality rate observed. Several authors reported reduced mortality rates in the presence of lower failed weaning attempts and improved extubation rates (Stawicki 2007; Putensen et al 2006; Robertson 2003; Ely et al 2001) and results from this study seem to support this theory.

It could be argued that the individualised CPAP programme used for this study was conservative compared to the protocols advocated by several authors (Ambrosino 2005; Grap et al 2003; Ely et al 2001; MacIntyre et al 2001), but the results achieved for successful extubation, decreased number of failed spontaneous breathing attempts and low mortality rate for the intervention group are encouraging. These results were obtained without adding any additional time to the overall MV days and therefore by implication any added risks to the patient.

5.1 CHALLENGES PERTAINING TO THE MULTI-DISCIPLINARY TEAM IN THE CURRENT STUDY

One of the strongest recommendations of the American College of Chest Physicians in their guidelines for weaning and discontinuation of ventilatory support (MacIntyre et al 2002 and 2001) was the use of non-physician health care professional driven weaning protocols in the absence of a dedicated fulltime intensivist. The current study was based on this recommendation and therefore a multi-professional team approach was used, utilizing nursing staff and physiotherapists. The attending physician merely determined the time to extubate the patient based on the data presented to him/her by the nursing staff and physiotherapists. It was interesting to observe that some physicians found it necessary to make small changes in the progression of the individualised CPAP programme, without any rational argument for the change, or to add some random screening tests such as their own MIP measurements. The researcher had to manage these small interprofessional tensions with care to ensure that the new protocol was effectively implemented. The occurrence of such changes in management was also documented by Lingard et al in 2004 and where anticipated by the researcher.

Throughout the duration of the study it was observed that the nursing staff experienced difficulty in accepting the responsibility of making decisions regarding implementation of the

protocol, even though it was pre-approved by all health-care professionals involved in the study. Brilli et al (2001) stated in the consensus report of the Society of Critical Care Medicine on leadership that defining clinical roles in the ICU is vital to ensure quality critical care in the ICU setting. They stated that when practicing in a multi-disciplinary setting, nurses are often faced with dealing with conflicting orders and unclear lines of both authority and responsibility for patient care. In the current study it was observed that the majority of nursing staff wanted to wait for the approval of the attending physician before placing the subjects on a SBT or continuing with the progression of the individualised CPAP programme. This hesitation could have added to the time that the subjects in the intervention group spent in stage two and three of MV, but is not believed to have affected the extubation success rate, the mortality rate or the failed SBT events reported in this study.

The nursing staff also showed some initial reluctance and resistance to screen subjects for SBT readiness as they were hesitant to add additional time constraints on their already tight time schedule. This reluctance and resistance resolved quickly once they realised the benefits of the programme for the subjects and when they observed how quick and easy the screening process was. Hawryluck et al (2002) reported on interdisciplinary tension in the delivery of health care in ICU, especially when professional roles were not clarified and when new protocols were implemented. Hawryluck et al (2002) reported that protection of perceived scope of practice was an important factor in interdisciplinary tension in the ICU as some professionals were reluctant to take on additional roles, or to share some roles with other interdisciplinary team members. The use of temporary nursing staff in ICU in the current study as well as the workload of the staff compromised compliance with the individualised CPAP programme at times. In some instances the period that subjects were kept on CPAP or the rest period was not followed exactly according to the protocol. The termination criteria for the individualised CPAP programme or SBT trial was ignored in only one case, leading to one failed SBT event in the intervention group. Due to the long duration of the study (one year) the researcher ensured that the staff were constantly reminded of the protocol and informed about the status of the study. New staff were informed and trained in the implementation of the protocol. McLean et al (2006) stated that engaging the multidisciplinary team in a clinical protocol change is an important factor to determine the successful implementation of adherence to such a protocol. This trend was also observed in this study.

Strict adherence to the protocol was of utmost importance to ensure that it was followed by all staff involved. Due to the busy daily schedule of the nursing staff the researcher had to be constantly involved to ensure adherence to the protocol. This should be taken into consideration if this protocol is implemented as a standard weaning protocol in any ICU.

Appointing a dedicated staff member as the weaning protocol manager (in the absence of a full time ICU physiotherapist) should be considered.

The results obtained from this study with regard to success rate of extubation, reduction in failed SBT events and mortality rate correlate with the findings reported by others that the use of a multidisciplinary team model in ICU care may reduce mortality and complications in critically ill patients (Garrubba, Turner and Grievenson 2009).

5.2 SIGNIFICANCE OF FINDINGS

To the researcher's knowledge this is the first experimental, prospective study of its kind in South Africa that has investigated the implementation of an individualised CPAP programme in preparation of the intubated adult patient for extubation. Other researchers (Chang et al 2005; Martin et al 2002; Rosario et al 1997) suggested that strategies such as inspiratory muscle training alone or combined with progressive spontaneous breathing periods in mechanically ventilated patients to improve respiratory muscle endurance may facilitate weaning. No studies that incorporated the principles of muscle rehabilitation in weaning protocols with regards to endurance, strength training and rest [as recommended by Noonan and Dean (2000)] could be found in the current literature for the management of the adult patient on MV. Rosario et al (1997) suggested that strategies that improved respiratory muscle endurance may facilitate weaning.

From the results of the current study, it can be assumed that there is a likelihood that the more time patients spend in stage 3 of MV, the less time they are likely to spend in stage 2 of MV. Spending more time in stage 3, in a well controlled manner, and less time in stage 2 may result in less diaphragmatic atrophy, and subsequent respiratory muscle weakness, as well as improved respiratory muscle endurance.

Although the respiratory muscle endurance of subjects was not tested in the current study, it would be reasonable to assume that the individualised CPAP program did protect subjects against failed spontaneous breathing and extubation attempts. It can be assumed that the respiratory muscles of the subjects in the intervention group were more efficiently managed, compared to the control group, to prevent low frequency fatigue and improved overall respiratory muscle endurance, hence the improved weaning outcomes. Therefore it appears that the effectiveness of the implementation of the muscle rehabilitation principles (specific adaptation to imposed demand, overload and individual differences principle) during the spontaneous breathing stage of a weaning protocol can have a positive impact on the weaning outcomes of adult patients on MV.

The improved extubation rate, decreased SBT failure and decreased mortality rate obtained from the results of this study correlate positively with the findings of authors such as Esteban et al (2007); Grap et al (2003); Ibrahim et al (2001) and Vitacca et al (2001). These authors reported that a systematic, well planned non-physician driven, weaning process for MV yielded the best results for patients and halved the rate of complications associated with MV. The implementation of such a weaning process, in the test setting and not necessarily the individualised CPAP part of the program could have been the reason for the improved weaning outcomes in this study. This statement is made based on the fact that there was no weaning management strategy in the test setting prior to the commencement of this study. It would be of interest to test the individualised CPAP program in a test setting where a systematic, well planned, non-physician driven weaning process is in place.

The mortality rate of the intervention group was 75.1% lower than the mortality rate of the control group which is significantly higher than the 12% improvement reported by Kahn et al (2010). The mortality rate of the control group was 33.3% and that of the intervention group was 8.3%; [(33.3 – 8.3)/33.3x100 =75.7%]. Kahn et al (2010) made the statement that in the absence of trained intensivists (similar to the current test setting) the use of a multidisciplinary approach to patient management in the ICU could reduce the mortality by a significant 12%. However, due to the fact that the full accurate SAPS II scores for the subjects and the exact cause for mortality were not recorded, it is not possible to claim that the individualised CPAP programme used in this study was the primary reason for the improved mortality rate in the intervention group. Due to the fact that a formal weaning program, with objective parameters, was introduced into a test setting where previously no weaning program was in place, the researcher acknowledges that this could have contributed to the improved mortality rate as well as having an effect on the other outcomes. The positive findings of this study with regard to weaning and extubation outcomes do however open a door for physiotherapists in South Africa to extend their scope of practice beyond the general scope of practice of physical rehabilitation and bronchial hygiene of this patient population as reported by Van Aswegen and Potterton (2005). It also demonstrates that physiotherapists could incorporate their expert knowledge of muscle rehabilitation and physiology into the weaning protocols of patients on MV, as suggested by Dean et al (2006), to prevent the complications of prolonged MV on the respiratory muscles.

Based on the results of this study the hypothesis outlined in chapter 3 which stated that the implementation of an individualised CPAP programme during stage 3 (the spontaneous breathing stage) of a weaning protocol will improve the preparation of a patient for extubation

and therefore improve the outcomes (successful stage three of MV, successful extubation and decreased mortality rate during MV) of extubation more so than the standard weaning procedure in adult subjects who are mechanically ventilated, can be accepted.

5.3 LIMITATIONS OF THE STUDY AND RECOMMENDATIONS FOR FUTURE TRIALS

The researcher acknowledges the fact that the study was limited to only one clinical setting. Confounding variables and other co-morbidities such as previous smoking, diabetes, existing cancer and renal failure were not recorded. This could have had an impact on the outcomes of this study. The researcher accepts the fact that the unique ICU environment (staff to patient ratios, experience of the multidisciplinary team and existing weaning protocols, to name but a few) as well as the vulnerability of the ICU population (pre-existing co-morbidities, SAPS II scores and MV and ICU acquired complications) make it impossible to claim that one factor alone influenced an outcome. Due to this uniqueness, the results of this study may not be able to be duplicated in another test setting, and it would not be accurate to generalise these findings to the general ICU population.

It was not possible to include disease severity as a confounding variable because two different disease severity scores were used by the nursing staff during the duration of this study. This was implemented without the prior knowledge of the researcher and instituted by the nursing management of the ICU that changed during the course of the study. The therapeutic assessment score (TAS) was initially used to classify disease severity in 2008 and in August 2009 it was changed to the APACHE score. The researcher also observed that disease severity was not always 100% accurately scored by the nursing staff. Although the demographic and confounding variables of the subjects in the two groups showed no statistically significant differences, closer monitoring, analysis and classification of these could have resulted in a more objective comparison between the groups and might have identified a mismatch between the two groups, if such a mismatch did exist.

The outcomes of this study should be tested in further randomised controlled trials with a larger sample size, where formal non-physician driven weaning protocols are already in place. This would allow the study to test the effect of an individualised CPAP program as compared to a standard non-physician driven weaning program, and will thereby exclude other factors that could impact on the results.

When using the individualised CPAP programme for the management and prevention of low frequency fatigue and ventilatory induced diaphragmatic dysfunction the following are recommended:

- A large portion of the undergraduate training programmes for physiotherapists in South Africa involves training and clinical reasoning in human anatomy, physiology, pathology and exercise science. For this reason, physiotherapists are well equipped to take a leading role in the prescription of the individualised CPAP programme to ensure that the respiratory muscles of the patient receive adequate rest and adequate training for both types of muscle fibres. The individualised CPAP programme should be tailor-made for each patient's unique clinical findings and screening results.
- Staff (nursing and physiotherapy) should take ownership of the programme and not be afraid to make weaning decisions based on objective tests such as RSBI and RSBI rate which proved to be reliable in the current study.
- In the absence of dedicated intensivists the attending physicians should allow the nursing staff and physiotherapists to make such decisions.

A brief conclusion of the current study will be given in chapter 6.

CHAPTER 6

6. CONCLUSION

The aim of the current study was to develop, implement and test the outcomes of an individualised CPAP protocol programme, utilizing the principles of muscle rehabilitation (daily step wise individualised progression according to the subjects needs and progress with adequate rest and recovery periods) for adult subjects who were mechanically ventilated. This was done by conducting an experimental, prospective, non-randomised, sequential study using two groups (n=48). Subjects in the control group (n=24) received the standard weaning management and the subjects in the intervention group (n=24) received an individualised CPAP programme, based on the principles of exercise physiology. The following outcomes were tested: a) time spent in stages 2 and 3 of MV, b) total days on MV, c) failure rate of the subject's ability to sustain spontaneous breathing in stage 3 of MV, d) mortality rate during stage 3 or within 48 hours after extubation and e) the rate of successful extubation.

Even with the limitations of the study mentioned in chapter five; namely non-randomised study design with a relatively small sample size limited to one test setting, there were positive results with respect to the primary outcomes of decreased failed spontaneous breathing attempts, improved extubation rate and a decrease in the mortality rate of the intervention group compared to those of the control group. There was no statistically significant differences between the two groups in the total time that was spent on MV in stage 2 (weaning stage) or the overall time spent on MV. There was a statistically significant difference in the time spent in stage 3 of MV (spontaneous breathing stage) as well as a significant decrease in the mortality rate and failure rate of the subjects in the intervention group's ability to sustain spontaneous breathing in stage 3 of MV. There was a positive difference in the rate of successful extubation between the two groups.

This study on the design and implementation of an individualised CPAP programme for adult subjects on mechanical ventilation was, to the author's knowledge, the first of its kind to be conducted in Witbank, in South Africa or internationally. Physiotherapists form part of a multidisciplinary team that is responsible for the care of critically ill patients in the ICU. Physiotherapists in South Africa are, due to their extensive training, well qualified to be involved in the care of these patients in ICU. In conclusion there seems to be a prominent role for physiotherapists to play in the prescription and implementation of such training programmes for patients on MV in order to improve the preparation of a patient for extubation and therefore

improve the outcomes (successful stage three of MV, successful extubation and decreased mortality rate during MV) of extubation in adult subjects who are mechanically ventilated.

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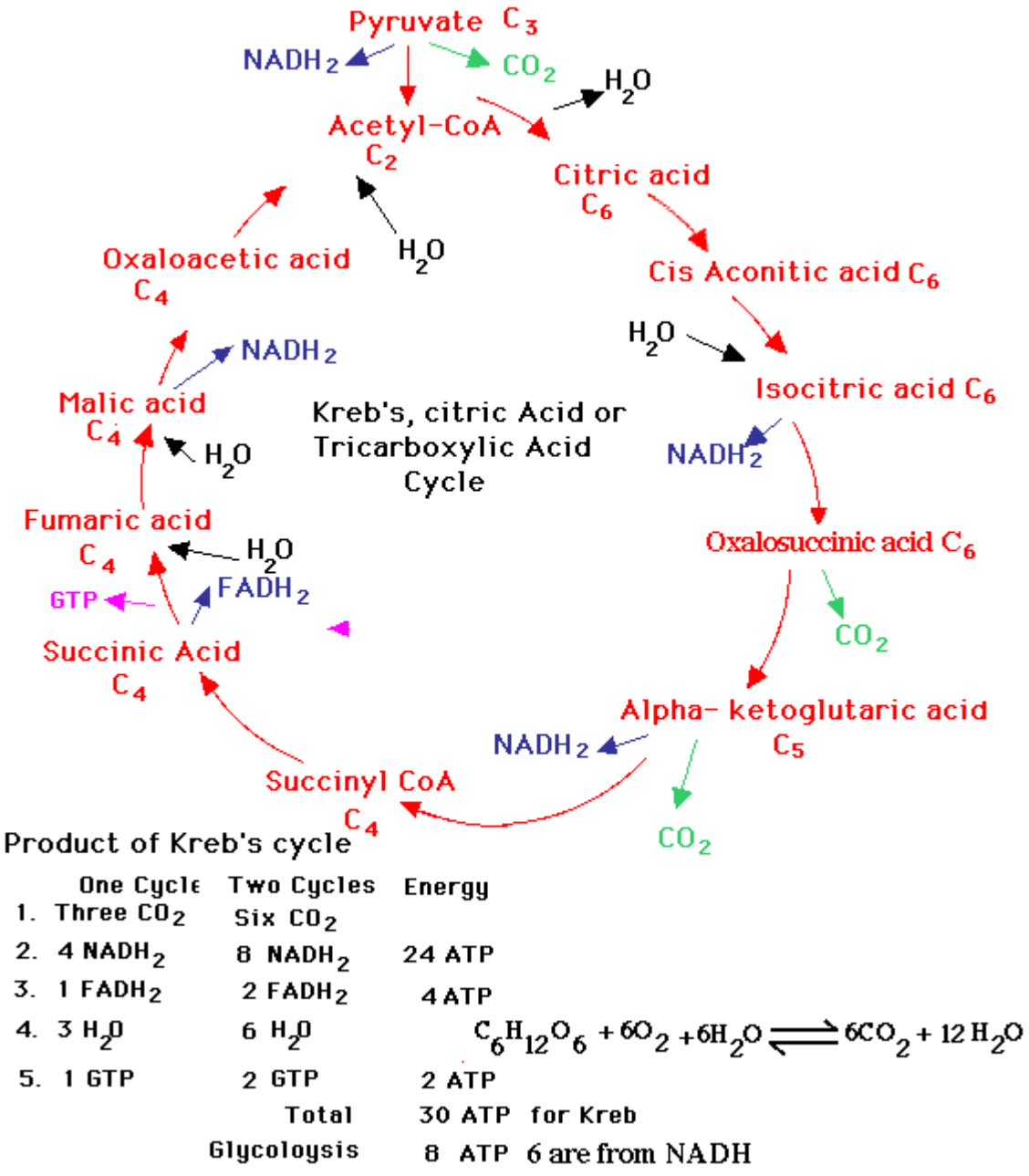
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APPENDIX 1

Figure 1: Krebs' Cycle



Product of Kreb's cycle

	One Cycle	Two Cycles	Energy
1.	Three CO_2	Six CO_2	
2.	4 $NADH_2$	8 $NADH_2$	24 ATP
3.	1 $FADH_2$	2 $FADH_2$	4 ATP
4.	3 H_2O	6 H_2O	
5.	1 GTP	2 GTP	2 ATP
		Total	30 ATP for Kreb
		Glycolysis	8 ATP 6 are from NADH

$$C_6H_{12}O_6 + 6O_2 + 6H_2O \rightleftharpoons 6CO_2 + 12\,H_2O$$

Figure 1. Krebs Cycle

APPENDIX 2

Baseline Data Collection Sheet

BASELINE DATA SHEET				
Patient Nr:	**Days in ICU**	**Days on MV**	**Hours in Stage 2 of MV**	**Hours in Stage 3 of MV**

APPENDIX 3

Screening Forms 1-3

WEANING PROTOCOL SCREENING TOOLS FOR
COSMOS LIFE HOSPITAL
ADULT INTENSIVE CARE UNIT

SCREEN 1: NURSES TO DO DAILY

All patients receiving mechanical ventilation are assessed by using screen 1 every day, and results are documented on the weaning assessment form.

Parameter	**Results**	
1. Hemodynamics stable?	**Yes**	**No**
2. Off vasopressors? (Adrenaline)	**Yes**	**No**
3. PaO_2/FiO_2 ratio > 150? (If ABG's not available: SaO_2> 95% on FiO_2 of 50% or less)	**Yes**	**No**
4. PEEP set at 8 cmH_2O or less?	**Yes**	**No**
5. Pressure support 10 or less?	**Yes**	**No**
6. Richmond Agitation – Sedation Scale: (RASS) –2 or higher?	**Yes**	**No**

If NO to questions 1, 3, 4, 5 or 6:

STOP!

Otherwise, ALWAYS proceed to screen 2

SCREEN 2: PHYSIOTHERAPIST/NURSE TO DO

1. **Rapid Shallow Breathing Index (RSBI)**
   Settings on ventilator
   - Flow trigger mode rate = 0
   - Pressure support = 0 cmH_2O
   - PEEP = 5cmH_2O

   Start measuring 1 minute after set up: At the end of 1 minute,

   - Respiratory rate (RR) = _____
   - Tidal Volume (V_t) =_____

   RSBI = RR / V_t =_____ 100 or less

YES	NO

2. **Maximum Inspiratory Pressure (MIP**) = _____

   Highest (MIP), measured over 30seconds: Higher than –20 cmH_2O

If NO to question 1:

STOP!

Rest patient until next day and reassess starting with SCREEN 1

If YES to question 1:

Proceed to spontaneous breathing trial

SCREEN 3: SPONTANEOUS BREATHING TRIAL (SBT)

Spontaneous breathing for up to 120 minutes through ventilator

Ventilator Settings:

- Flow trigger mode set to 1
- Pressure support to between 8 cmH_2O or less
- PEEP up to 5cm H_2O

Time from start of SBT to termination: _____minutes.

Reason for termination: _____

_____

Progress to Individualised CPAP programme prescribed by physiotherapist.

NB: TERMINATION CRITERIA:

- Respiratory rate >35/min for 5 minutes or more
- SAO_2 <90%

  Heart rate >140/min, or sustained increased of 20% greater than baseline for longer than 30 minutes
- Systolic blood pressure >180mmHg or <90mmHg for longer than 30 minutes
- Increased anxiety

APPENDIX 4

Rapid Shallow Breathing Index Protocol

PROTOCOL FOR RAPID SHALLOW BREATHING INDEX (RSBI)

1. Set the ventilator on:
   - Flow trigger mode rate = 0
   - Pressure support = 0
   - PEEP = 5 cmH_2O

2. Start measuring 1 minute after set up: At the end of 1 minute, record the following:
   - Respiratory rate (RR) = _____
   - Tidal Volume (V_t) =_____
   - RSBI = RR / V_t =_____ 100 or less

3. A RSBI of 100b/min/l or less is an indication that the patient is ready to be put on a spontaneous breathing trial.

APPENDIX 5

Maximum Inspiratory Pressure Measurement Protocol

PROTOCOL TO MEASURE THE MAXIMUM INSPIRATORY PRESSURE (MIP)

Ref: Vela Ventilator Systems. Operators Manual: pg. 79 L1533/ Revision E

1. Ventilator settings: CPAP mode.
   PEEP = 8cmH_2O or below
   Pressure support 10cmH_2O or below.

2. MIP is accessed through the Screen Select Box.
   a. Touch the screen indicator in the top centre of the Main Screen display.
   b. The Screen box will be displayed.
   c. Select MANEUVER from the selection box.
   d. Press and hold the touch screen button for 30 seconds, while encouraging the patient to inhale as deeply as possible.

3. The message bar in the lower left hand corner of the touch screen displays the starting pressure (Pstart, the airway pressure (Paw) and the Maximum Inspiratory Pressure (MIP)

   Pstart…….Paw……MIP……cmH_2O

   Record all 3 measurements on the screening form.

4. When the button is released or 30 seconds pass, the ventilator resumes ventilation and the highest MIP value is displayed.

APPENDIX 6

Individualised Continuous Positive Airway Pressure Program

INDIVIDUALISED SPONTANEOUS BREATHING PROTOCOL

SPONTANEOUS CPAP BREATHING TRIAL (SBT1) TIME Peep at 5 Pressure support at 8 or less	CPAP TIME 75% of SBT1 time Individual PEEP and Pressure support settings.	REST PERIOD. Back to pre - SBT Ventilatory settings.	T-PIECE TIME 75% of CPAP Time	REST PERIOD Back to pre - SBT Ventilatory settings.	REPEAT X DURING DAY
Less than15 minutes	10 min	180 min	Not ready for T-Piece	NA	**3**
15 Minutes	10 min (11.25 min)	120 min	Not Ready for T-Piece	NA	**3**
30 Minutes	20 min (22.5 min)	90 min	15 min	90 min	**3**
60 Minutes	45 min	60 min	30 min	60 min	**3**
90 Minutes	65 min (67.5 min)	60 min	50 min	60 min	**3**
120 Minutes	90 min	60 min	70 min	60 min	**3**

DAILY PROGRESSION SCHEDULE IF PATIENT WERE STABLE ON THE DAY'S SCHEDULE:

- CPAP time will be increased by 50%.
- Rest periods will be decreased by 25%
- T-Piece time will be increased by 20%
- **Patients will be tested BD to determine the ICPAP for the night. If the RSBI have not worsen by more than 20% after 12 hours of ICPAP the patient could continue on the ICPAP for the night.**

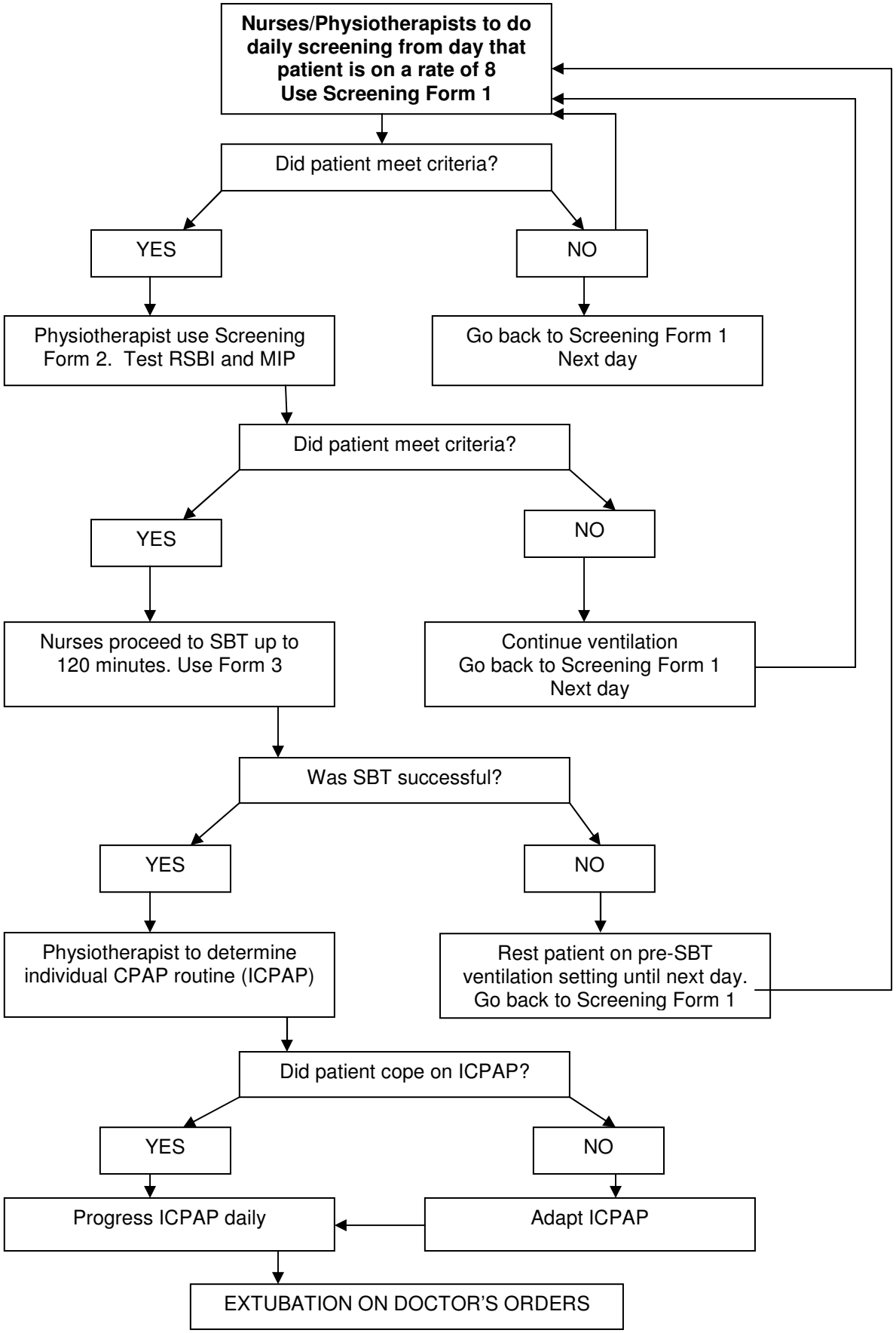
TERMINATION CRITERIA: Return patient to pre-spontaneous breathing trial ventilatory settings if any one of the following occurs:

- Respiratory rate >35/min for 5 minutes or more
- SaO_2 <90% for longer than 10 minutes or more
- Heart Rate >140/min, or sustained increase of 20% greater than the baseline for longer than 10 minutes
- Systolic blood pressure >180mmHg or <90mmHg for longer than 10 minutes
- RSBI rate of <20%

APPENDIX 7

Weaning Flow Chart

WEANING PROTOCOL FLOW CHART



APPENDIX 8

Patient Information Sheet

INFORMATION BROCHURE

Group One

THE IMPLEMENTATION OF AN INDIVIDUALISED CONTINUOUS POSITIVE AIRWAY PRESSURE PROGRAM IN PREPARATION OF THE INTUBATED ADULT PATIENT FOR EXTUBATION

Dear _____

(Name of potential patient/guardian)

My name is Wilma Erasmus and I am presently registered as a Physiotherapy masters student at the University of the Witwatersrand in the Faculty of Health Sciences. I hope to conduct a research project and would like to ask you to consent to my including your family member as a sample patient in my research project.

The aim of this study is to determine if adult patients who are on a ventilator will be able to be weaned quicker from the ventilator if a step-by-step weaning protocol is followed.

The above will be done with the full participation of the attending physician, physiotherapists and nursing staff in the intensive care unit.

Patients that require mechanical ventilation for various medical reasons get support from the ventilator in different ways, by number of breaths from the machine, the pressure support to keep the lungs open and the percentage oxygen to ensure adequate oxygen to the body cells.

During mechanical ventilation the muscles that assist in breathing become weak. This weakness causes patients to have difficulty to breathe on their own.

Weaning from the ventilator can depending on the patient's condition, take hours, days or in severely ill patients even months. Weaning is practised every day and is not unique to this research study.
The uniqueness of this study is that the patient is put on an individual spontaneous breathing program, developed specifically for each patient, depending on the strength and endurance of the patient's respiratory muscles.

Your family member will be part of the control Group and will receive the normal weaning protocol and only his/her data will be used as control data.

There is no additional risk or discomfort to the patient participating in this clinical trial.

The potential benefits to future patients are: decreased time spent on the ventilator, decreased ICU cost, decreased risk of complications such as ventilator acquired infections.
The ICU staff will gain additional knowledge in the future management of weaning of adult patients from the mechanical ventilator.

Participation in this study is voluntary, and even after the study begins you or your relative can decide to terminate your participation at any point, which will have no effects on the services that you or your relative may receive from this institution or the health care providers. Normal mechanical ventilation strategies will be applied in such cases.

All information and data gathered will be handled with strict confidentiality. No reports of the study will identify your or your relative in any way. Results of the study will be given to you should you wish.

The appropriate people and research committees of the University of the Witwatersrand and Cosmos Life Hospital have approved the study and its procedures.

Thank you for taking the time to read this information sheet. Should you have any further questions about the study or your rights as a study participant, please feel free to contact me at:

Highveld Medical Centre
22 Frans Quass Street
Ext 12
Witbank
Telephone number: 013 656 4176.
Cell 0832307307

INFORMATION BROCHURE

Group Two

THE IMPLEMENTATION OF AN INDIVIDUALISED CONTINUOUS POSITIVE AIRWAY PRESSURE PROGRAM IN PREPARATION OF THE INTUBATED ADULT PATIENT FOR EXTUBATION

Dear _____

(Name of potential patient/guardian)

My name is Wilma Erasmus and I am presently registered as Physiotherapy masters student at the University of the Witwatersrand in the Faculty of Health Sciences I hope to conduct a research project and would like to ask you to consent to my including your family member as a sample patient in my research project.

The aim of this study is to determine if adult patients who are on a ventilator will be able to be weaned quicker from the ventilator if a step-by-step weaning protocol is followed.

The above will be done with the full participation of the attending physician, physiotherapists and nursing staff in the intensive care unit.

Patients that require mechanical ventilation for various medical reasons get support from the ventilator in different ways, by number of breaths from the machine, the pressure support to keep the lungs open and the percentage oxygen to ensure that enough oxygen reach the body cells.

During mechanical ventilation the muscles that assist in breathing become weak. This weakness causes patients to have difficulty to breathe on their own.

Weaning from the ventilator can depending on the patient's condition, take hours, days or in severely ill patients even months. Weaning is practised every day and is not unique to this research study.
The uniqueness of this study is that the patient is put on an individual spontaneous breathing program, developed specifically for each patient, depending on the strength and endurance of the patient's respiratory muscles.

The physiotherapist and the staff will screen the patient daily to determine the patient's readiness to be put on the program.

- The results of this program will be monitored daily and presented to the attending doctor, who will determine the readiness of the patient for extubation (patient removed from the ventilator).

There is no additional risk or discomfort to the patient participating in this clinical trial.

The potential benefits to the patients are: decreased time spent on the ventilator, decreased ICU cost, decreased risk of complications such as ventilator acquired infections.
The ICU staff will gain additional knowledge in the future management of weaning of adult patients from the mechanical ventilator.

Participation in this study is voluntary, and even after the study begins you or your relative can decide to terminate your participation at any point, which will have no effects on the services that you or your relative may receive from this institution or the health care providers. Normal mechanical ventilation strategies will be applied in such cases.

All information and data gathered will be handled with strict confidentiality. No reports of the study will identify your or your relative in any way. Results of the study will be given to you should you wish.

Due to the strict screening tools and observation tools that will be implemented during this study there is no additional risk for injury as a direct result of the research activity.

The appropriate people and research committees of the University of the Witwatersrand and Cosmos Life Hospital have approved the study and its procedures.

Thank you for taking the time to read this information sheet. Should you have any further questions about the study or your rights as a study participant, please feel free to contact me at:

Highveld Medical Centre
22 Frans Quass Street
Ext 12
Witbank
Telephone number: 013 656 4176.
Cell 0832307307

APPENDIX 9

Individualised Continuous Positive Airway Pressure Schedule

DAILY INDIVIDUALISED SPONTANEOUS BREATHING SCHEDULE

PATIENT STICKER: DATE: _____ PHYSIOTHERAPIST: _____

CPAP TIME:	**REST PERIOD:**	**T-PIECE/T- MASK TIME:**	**REST PERIOD:**
PEEP:	PEEP: Rate:		PEEP: Rate:
Pressure Support:	Pressure Support:		Pressure Support
On: Off:	On: Off:	On: Off:	On: Off:
On: Off:	On: Off:	On: Off:	On: Off:
On: Off:	On: Off:	On: Off:	On: Off:

TERMINATION CRITERIA: Return patient to pre-spontaneous breathing trial ventilatory settings if any one of the following occurs.

- Respiratory rate >35/min for 5 minutes or more
- SaO_2 <90% for longer than 5 minutes or more
- Heart Rate >140/min, or sustained increase of 20% greater than the baseline for 10 minutes or longer
- Systolic blood pressure >180mmHg or < 90mmHg for 10 minutes or longer
- Increased anxiety

APPENDIX 10

Data Capture Sheets A and B

GROUP ONE: DATA COLLECTION SHEET

Study Number: _____

Age:_____

Sex: M / F

HIV Status: + / - / Unknown

1st TAS Score:_____

SAPS II Admission Criteria:

Medical Condition ☐

Elective Surgery ☐

Emergency Surgery ☐

Smoking: Yes / No / Unknown

Date admitted to ICU : ____/__/20_____

Ventilation start date : ___/__/20_____

Starting date of stage 2: ___/__/20_____

Starting date of stage 3: __/__/20_____

Failed stage 3 attempts: _____

Date of Extubation : _____

Total ventilated days : _____

Total ICU cost : _____

Total days in ICU : _____

Total stage 1 hours : _____

Total stage 2 hours : _____

Total stage 3 hours : _____

Reason : _____

Successful: Yes / No

GROUP TWO: DATA COLLECTION SHEET

Study Number: _____

Age:_____ SAPS II Admission Criteria:

Sex: M / F Medical Condition: ☐

HIV Status: + / - / Unknown Elective Surgery: ☐

TAS Score:_____ Emergency Surgery ☐

Smoking: Yes / No / Unknown

Date admitted to ICU :	____/__/20_____	Total days in ICU	: _____
Ventilation start date :	___/__/20_____	Total stage 1 hours	: _____
Starting date of stage 2:	___/__/20_____	Total stage 2 hours	: _____
Starting date of stage 3:	__/__/20_____	Total stage 3 hours	: _____
Failed stage 3 attempts:	_____	Reason	: _____
Date of Extubation :	_____	Successful	: Yes / No
Total Ventilated days :	_____		
Total ICU Cost :	_____		

APPENDIX 11

Ethical Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Erasmus

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080952**
PROJECT	The Application of the Basic Principles of Exercise Phusiology in Preperation of the Intubated Adult Patient for Extubation
INVESTIGATORS	Ms W Erasmus
DEPARTMENT	Physiotherapy Department
DATE CONSIDERED	08.09.26
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.09.29 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr H Van Aswegen

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 12

Permission Letter from Cosmos Life Hospital, ICU Steering Committee and Management to Perform Study

Wilma,

Ons erken graag ontvangs van jou brief gedateer 03 Junie 2008.

Beide Mev. Bezuidenhout en Mev. Van der Merwe verleen hulle toestemming vir jou versoek.

Baie sterkte en lekker dag.

Helga Greyling
Hospital Management Secretary

Life Cosmos Hospital
HEALTH CARE

Tel : +27 13 653 8145
Fax : +27 13 653 8005 or 086 677 6510
Mobile: 082 657 6334
Email : Helga.greyling@lifehealthcare.co.za
Website: www.lifehealthcare.co.za

The Hospital Manager
Cosmos Life Hospital
Witbank
1035

03 June 2008

Dear Mrs Bezuidenhout

RE: PERMISSION TO OBTAIN DATA FROM PATIENT FOR RESEARCH PURPOSES

I am currently enrolled as a student for the Masters Degree in Physiotherapy at the University of Witwatersrand. I am doing this degree via dissertation. My research is focussed on the weaning protocols of adult ventilated patients.
The study will be an experimental, prospective, nonrandomized, cohort study on two Groups.

I therefore ask the permission of the hospital management to obtain data from patients that have been mechanically ventilated in Cosmos Life Adult ICU from 1 July 2007 to 31 December 2007.

This data will be used to establish base line outcome data that will be compared with the same data during the clinical trial.

- Data needed is:
- Age of patient.
- ICD 10 code of patient.
- Therapeutic Assessment Score (TAS)
- Total number of days in ICU
- Total number of days ventilated
- Total number of failed spontaneous breathing episodes while ventilated.

Ethical clearance will be obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (HREC) prior to commencing of the study.

A research assistant will gather the data at the hospital. All patients' information will be made anonymous and data will only be available to the academic staff at the University that is helping with the research study. All information will be stored and handled as laid down by the HREC.
.
Your earliest attention to this request will be highly appreciated.

Kind Regards

Wilma Erasmus
Physiotherapist
013 656 4176

APPENDIX 13

Research Assistant: Letter of Appointment

LETTER OF APPOINTMENT

JOB TITLE: Research Assistant

This letter serves to state that Corne Potgieter will be appointed as a research assistant for researcher Wilma Erasmus, physiotherapy masters student Wits from 1 December 2008 till the research project has been completed.

Duties:

Allocate study numbers to patient's hospital numbers.

Collect and capture data of Group A (control Group) and Group B (intervention, experimental Group) on the data sheets provided.

Collect the data of the baseline data of patients in ICU for 2008.

All data will be accurately captured from the patients' daily hospital files.

Patient information will be kept confidential and will only be made available to the researcher.

Payment:

An hourly rate of R85 will be paid. A log will be kept on hours spend on the project. Payment will be made at the end of each month.

I…….hereby declare that there is no conflict of interest due to my appointment as research assistant.

Signed on …./ …./2008 at……..

…… ……

Researcher: W Erasmus Research Assistant.

APPENDIX 14

Subject Informed Consent Letter

THE IMPLEMENTATION OF AN INDIVIDUALISED CONTINUOUS POSITIVE AIRWAY PRESSURE PROGRAM IN PREPARATION OF THE INTUBATED ADULT PATIENT FOR EXTUBATION

FAMILY MEMBER / RELATIVE

CONSENT FORM

I _____ (name) the _____ (relationship)

of the patient give permission to be included in the study.

I have read with understanding the content of the information sheet and I have been given the opportunity to ask questions I might have regarding the procedure and my consent to my being included in the study.

_____ _____

Date Signature

1. _____ (Witness)

THE IMPLEMENTATION OF AN INDIVIDUALISED CONTINUOUS POSITIVE AIRWAY PRESSURE PROGRAM IN PREPARATION OF THE INTUBATED ADULT PATIENT FOR EXTUBATION

RETROSPECTIVE PATIENT CONSENT FORM

I, _____(name of the patient) understand that

my relative, _____ (name of relative), has given consent to my being included in the study and hereby give consent for the information obtained to be used in the study.

I have read with understanding the content of the information sheet and I have been given the opportunity to ask questions I might have regarding the procedure and my consent to my being included in the study.

_____ _____

Date Signature

1. _____ (Witness)

APPENDIX 15

Richmond Agitation Sedation Scale (RASS)

Richmond Agitation-Sedation Scale (RASS)

Score and 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 behavior towards staff
+ 2 Agitated	Frequently non-purposeful movement or patient-ventilator dyssychrony
+ 1 Restless	Anxious or apprehensive but movements not aggressive or vigorous
0 Alert and calm	
- 1 Drowsy	Not fully alert, but sustained (>10 Sec) awakening, with eye contact, to voice
- 2 Light sedation	Briefly(<10 sec) 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 do have movement to physical stimulation
- 5 Un-arousable	No response to voice or physical stimulation

Procedure:

1. Observe the patient. Is the patient alert and calm? (Score 0) Does the patient have behaviour consistent with restlessness or agitation? (Score +1 to +4)

2. If the patient is not alert, in a loud speaking voice, state the patient's name and direct the patient to open eyes and look at you.
   Repeat once if needed. Can prompt the patient to continue looking at you.

3. If the patient does not respond to voice, physically stimulate him or her by shaking his/her shoulder. If no response to shaking, do a sternum rub.