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INSPIRATORY MUSCLE TRAINING TO ENHANCE RECOVERY FROM INVASIVE MECHANICAL VENTILATION

Bernie Bissett

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Abstract

Inspiratory muscle weakness is a consequence of prolonged mechanical ventilation and may contribute to the residual physical disability which has been observed in intensive care survivors. Inspiratory muscle weakness is associated with duration of mechanical ventilation, with those ventilated for 7 days or longer most at risk of developing both strength and endurance deficits.

Specific resistance training of the inspiratory muscles (inspiratory muscle training) improves inspiratory muscle strength and endurance in normal people, athletes and patients with a wide variety of underlying pathologies. Mechanisms of improvement include proliferation of both Type 1 and Type 2 inspiratory muscle fibres, enhanced metabolism resulting in reduced lactate production, attenuation of a fatigue-induced metaboreflex, adaptations to neural pathways and modulation of the perception of dyspnoea. Furthermore, inspiratory muscle training enhances exercise tolerance and reduces dyspnoea in both patients and athletes, while improving quality of life for patients with chronic lung or heart disease.

There is a lack of evidence for inspiratory muscle training in intensive care patients, despite the potential benefits of training in this group. This project explores the feasibility, safety and efficacy of inspiratory muscle training in intensive care patients who have been mechanically ventilated for 7 days or longer, as this subset of patients is most likely to demonstrate inspiratory muscle weakness and therefore benefit from specific training. This project includes patient-centred outcome measures, as most studies of inspiratory muscle training to date have focused solely on impairments, rather than the patient experiences of quality of life, physical function or dyspnoea.

Study 1 establishes the safety and feasibility of high-intensity interval-based inspiratory muscle training in selected ventilator-dependent patients. Across 195 inspiratory muscle training sessions, there were no adverse events recorded during or immediately following the treatment. No significant changes were observed in heart rate, blood pressure, respiratory rate or oxygen saturation. Furthermore, mean training pressures increased by a mean difference of 18.6 cm H_2O across the 10 patients studied. Thus Study 1 confirms that inspiratory muscle training is safe in selected ventilator-dependent patients.

At time of project design, there was a lack of established outcome measures to assess global physical function in intensive care patients. Study 2 explores the clinimetric properties of the Acute Care Index of Function (ACIF) in a heterogeneous group of intensive care patients. Study 2 demonstrates that the ACIF has excellent inter-rater reliability (ICC 0.94 for total ACIF scores), and correlates well with the ICU Mobility Scale (r=0.84). Moreover, an ACIF score of less than 0.40 at intensive care discharge predicts discharge from hospital to a destination other than home (sensitivity 0.78). Thus Study 2 confirms the reliability and validity of ACIF as a tool to measure physical function in Studies 3, 4 and 5.

Study 3 is an observational study that describes the residual impairments of inspiratory muscle strength and endurance in a cohort of 43 patients recently weaned from mechanical ventilation. In this group, 37% demonstrated impaired inspiratory muscle endurance (fatigue resistance index < 0.80), while mean strength scores were only 38% of predicted values (mean 38.6, SD 19.7). This study also captured deficits in physical function, with mean ACIF score of 0.40/1.00, and raised perception of exertion both at rest (1.95/10) and during exercise (3.40/10). Thus even in an intensive care unit where minimal sedation, early rehabilitation and spontaneous modes of ventilation are the norm, patients recently weaned from mechanical ventilation have major residual impairments and functional deficits.

Study 4 is a randomised trial of high-intensity inspiratory muscle training in patients recently weaned from mechanical ventilation. Using concealed allocation, blinded outcome assessors and intention-to-treat analysis, Study 4 measures the effects of 2 weeks of inspiratory muscle training (in addition to usual care) compared to usual care. Patients in the experimental group demonstrated greater improvements in inspiratory muscle strength (mean difference 11%), but not endurance, while quality of life improved more in the experimental group than the control (mean difference 12%). Improvements in physical function and dyspnoea were equivalent. Thus 2 weeks of inspiratory muscle training improves inspiratory muscle strength and quality of life in the post-weaning period.

Finally, Study 5 is a protocol for a randomised trial of inspiratory muscle training performed by patients while mechanically-ventilated. Study 5 measures the impact of inspiratory muscle training on duration of mechanical ventilation, as well as residual inspiratory muscle strength and endurance, quality of life, physical function and perceived exertion.

The clinical implications of this project are that inspiratory muscle training can be used in the post-weaning period to ameliorate respiratory muscle weakness, which may enhance quality of life for patients mechanically ventilated for seven days or longer. Furthermore, the ACIF can be utilised in intensive care patients to map the improvement trajectory and predict likely hospital discharge destination. Thus this project contributes to the body of knowledge regarding the rehabilitation of intensive care patients, providing feasible strategies to enhance patient care.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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Publications during candidature

PUBLISHED PAPERS RELATING TO THIS THESIS (Journal Articles)

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- **Bissett B**, Leditschke IA, Paratz J, Boots R (2012). *Protocol: Inspiratory Muscle training for Promoting Recovery and Outcomes in Ventilated patients (IMPROVe): a randomised controlled trial.* BMJ Open **2**;2 (2):e000813.

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- Leditschke IA, Green M, Irvine J, **Bissett B**, Mitchell IA (2012). *What Are the Barriers to Mobilising Intensive Care Patients?* Cardiopulmonary Physical Therapy Journal **23** (1):26-29.

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- 'Respiratory muscle fatigue following successful weaning from mechanical ventilation'. 7th International Physical Medicine and Rehabilitation Conference, San Diego USA 2014 (***Invited Speaker)***

- 'Sports medicine meets ICU: why you should train your patient like an athlete.' Australia New Zealand Intensive Care Society Conference, Hobart 2013 (***Invited Speaker)***

- 'Inspiratory muscle training and ventilator weaning'. Australia New Zealand Intensive Care Society Conference, Hobart 2013 (***Invited Speaker)***

- 'How much puff is enough?' College of Intensive Care Annual Meeting, Canberra 2011 (***Invited Speaker)***

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Author Bissett (Candidate)	Wrote and edited paper and created conceptual framework (70%)
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Author Bissett (Candidate)	Designed experiments, collected data, analysed data, wrote and edited paper (70%)
Author Leditschke	Designed experiments, data analysis, reviewed and edited paper (25%)
Author Green	Collected data, reviewed and edited paper (5%)

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Author Green	Designed experiments, collected data, reviewed and edited paper (5%)
Author Marzano	Collected data, reviewed and edited paper (5%)
Author Byrne	Collected data, reviewed and edited paper (5%)
Author Leditschke	Designed experiments, analysed data, reviewed and edited paper (10%)
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Author Neeman	Supervised data analysis, reviewed and edited paper (5%)
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Author Leditschke	Designed experiments, reviewed and edited paper (25%)
Author Paratz	Designed experiments, reviewed and edited paper (10%)
Author Boots	Designed experiments, reviewed and edited paper (5%)

Contributions by others to the thesis

The PhD candidate Bernie Bissett was responsible for the thesis, including all ethical approvals, grant acquisitions, registration of trials, study design, selection of outcome measures, data collection, statistical analysis, preparation of article manuscripts and the thesis. However, over the past 5 years the following people have made a significant contribution to the work presented in this thesis:

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LIST OF ABBREVIATIONS

ACIF Acute Care Index of Function

APACHE II Acute Physiology and Chronic Health Evaluation II

COPD Chronic obstructive pulmonary disease

EQ5D EuroQol (Health-related quality of life questionnaire)

FRI Fatigue resistance index

ICU Intensive Care Unit

IMS ICU Mobility Scale

IMT Inspiratory muscle training

MIP Maximum inspiratory pressure

MV Mechanical ventilation

RPE Rate of perceived exertion (dyspnoea)

SF36 Short Form 36 (health-related quality of life questionnaire)

CHAPTER 1: INTRODUCTION

Sections of this chapter have been published as a narrative review in the peer-reviewed journal Anaesthesia and Intensive Care and are reproduced with permission (Appendix C):

http://www.ncbi.nlm.nih.gov/pubmed/22417017

Bissett B, Leditschke IA, Paratz J, Boots R. (2012) *Respiratory dysfunction in ventilated patients: can inspiratory muscle training help?* Anaesthesia and Intensive Care **40** (2):236-46.

OUTLINE OF INTRODUCTION:

RATIONALE OF THE PROJECT

RESPIRATORY DYSFUNCTION IN VENTILATED PATIENTS

- Inspiratory muscle changes with mechanical ventilation
- Muscle weakness and failure to wean
- Polyneuropathy
- Pharmacological effects
- Nutrition
- Psychological factors
- Indications for inspiratory muscle training

MECHANISM OF INSPIRATORY MUSCLE TRAINING

- Definition of inspiratory muscle training
- Mechanisms of improvement with inspiratory muscle training

EFFICACY OF INSPIRATORY MUSCLE TRAINING IN OTHER POPULATIONS

- Chronic obstructive pulmonary disease
- Athletes and healthy people

INSPIRATORY MUSCLE TRAINING IN VENTILATOR-DEPENDENT PATIENTS

- Evidence for inspiratory muscle training in ventilator-dependent patients
- Psychological implications of inspiratory muscle training in ventilator-dependent patients
- Safety and feasibility of inspiratory muscle training in ventilator-dependent patients
- Links between respiratory dysfunction and inspiratory muscle training for ventilator-dependent patients

OUTLINE OF THE THESIS

RATIONALE OF THE PROJECT

Modern intensive care saves lives. In 2012 – 2013 more than 160 000 adults and children were admitted to intensive care units across Australia and New Zealand, and while 5.8% of patients died in intensive care, 74% were ultimately discharged home (ANZICS Centre for Research Outcome 2014). With many patients now surviving intensive care and returning to the community, the burden of intensive care survivorship has been examined. In a longitudinal study from the United States of America in 2010 (Unroe et al., 2010) the mean costs of one year of intensive care survivorship were estimated to be US$306 135, with 67% of patients readmitted to hospital at least once in that period. With increasing numbers of intensive care survivors around the world, these costs cannot be ignored.

The cost burden of intensive care survivorship can be better understood in terms of the residual physical and cognitive impairments affecting intensive care survivors. In patients with acute lung injury managed in intensive care, measures of physical and cognitive activity at 12 months following intensive care admission are approximately 25% of predicted values(Needham et al., 2013). Even at five years following intensive care admission, objective measures of physical activity in survivors of acute respiratory distress syndrome only improve to a mean of 76% of predicted values(Herridge et al., 2011). The longer term outcomes are even worse for intensive care survivors aged over 70, with more than half experiencing functional decline or early death (within 30 days of hospital admission) following critical illness(Ferrante et al., 2015). As described in an editorial by Iwashyna(2010):

> *"Distracted by the high mortality rate of critical illness, we tend to overlook the essential fact that most patients survive the intensive care unit. Every year, millions of patients are discharged from the ICU to face the challenges of critical illness survivorship – the complex burdens and legacies of surviving a potentially fatal disease, often after harsh and painful treatment."*

Invasive mechanical ventilation may be considered one such 'harsh and painful treatment' that saves lives. Of those admitted to intensive care in Australia and New Zealand from 2012 to 2013, 39% required invasive mechanical ventilation (ANZICS Centre for Outcome Resource ANZICS, 2014). Whilst unarguably life-saving for many, mechanical ventilation has deleterious consequences for respiratory muscle function which may lead to ventilator-dependence. Within just 70 hours of intubation, invasive controlled mechanical ventilation

results in diaphragmatic catabolism(Levine et al., 2003). This catabolism manifests as respiratory muscle weakness which is detectable whilst patients are ventilated(De Jonghe et al., 2007) and persists even following successful weaning from mechanical ventilation(Chang et al., 2005a, Bissett et al., 2015b). This respiratory muscle weakness may contribute to the phenomenon of difficult weaning from mechanical ventilation(Bissett et al., 2012a), leading to prolonged intensive care stays. As intensive care is expensive (e.g. $4490 per day (St Vincent's Hospital, 2015)), any intervention which may at least in part ameliorate respiratory muscle weakness, and consequent ventilator-dependence and potential long-term disability, deserves exploration.

Over the past 40 years, sports scientists have explored the potential of inspiratory muscle training to enhance the strength and endurance of inspiratory muscles. Inspiratory muscle training provides resistance on inspiration and unimpeded expiration, thereby providing a training stimulus isolated to the inspiratory muscles. There is now unequivocal evidence that specific high-intensity inspiratory muscle training leads to increased inspiratory muscle strength in a variety of athletes and healthy individuals(Volianitis et al., 2001, Klusiewicz et al., 2008, Riganas et al., 2008, Gething et al., 2004b, Johnson et al., 2007, Sonetti et al., 2001, Kilding et al., 2010, Williams et al., 2002, Inbar et al., 2000, McConnell and Sharpe, 2005, Chatham et al., 1999, Enright et al., 2006), and these improvements have translated into performance benefits in some endurance sports including rowing(Volianitis et al., 2001), cycling(Johnson et al., 2007) and running(Leddy et al., 2007). Similarly, in patients with chronic obstructive lung disease, inspiratory muscle training increases inspiratory muscle strength, reduces dyspnoea and improves exercise tolerance(Shoemaker et al., 2009). It is somewhat surprising that in intensive care patients, where inspiratory muscle weakness has been identified, there is little evidence regarding the efficacy of inspiratory muscle training.

Thus, drawing primarily on the lessons learned from sports medicine, the rationale of this thesis is to explore whether inspiratory muscle training is safe and feasible in intensive care patients, and determine whether inspiratory muscle training enhances the outcomes of intensive care survivors. These studies will contribute to the existing body of knowledge in intensive care from a pragmatic and patient-centred perspective, including a focus not just on measures of muscle strength and endurance, but also quality of life, dyspnoea and physical activity. With increasing numbers of patients surviving intensive care, and limited resources in financially-constrained healthcare systems around the world, the findings of

this work have direct implications for the prioritisation of interventions used by physiotherapists in the modern intensive care unit.

RESPIRATORY DYSFUNCTION IN VENTILATED PATIENTS

Ventilator-dependence is a significant burden for both individuals and health systems. Prolonged mechanical ventilation is associated with higher mortality, poor functional outcomes, lower quality of life and higher incidence of nursing home placement(Cox et al., 2007, Douglas et al., 2002). In this context, there has been surprisingly little research into the mechanisms of ventilator-dependence or treatment strategies to facilitate liberation from mechanical ventilation.

There is mounting evidence that mechanical ventilation itself results in pathological changes to the respiratory system which may contribute to prolonged ventilator-dependence and the clinical phenomenon of difficult weaning(Ambrosino and Gabbrielli, 2010). Potential contributors to ventilator-dependent respiratory dysfunction include inspiratory muscle weakness, polyneuropathy, pharmaceutical influences and nutritional and psychological factors.

Inspiratory muscle changes with mechanical ventilation

Muscle atrophy

Animal studies have clearly demonstrated that controlled mechanical ventilation results in measurable changes to the diaphragm. In a study of rats mechanically ventilated for 18 hours(Shanely et al., 2002) atrophy of both Type 1 and Type 2 muscle fibres was detected, with greater atrophy of Type 2 fibres, and a concurrent increase in diaphragmatic protease activity and oxidative stress, suggesting muscle catabolism. Another study using a rodent model(Powers et al., 2002), which rigorously excluded any contribution of phenobarbital to muscle changes, found that 12 hours of controlled mechanical ventilation resulted in an 18% reduction in diaphragmatic force, whereas 24 hours resulted in a 46% reduction. These studies indicate that a dose-dependent relationship between duration of ventilation and subsequent weakness is likely. Extrapolation of these results to humans is limited by the infrequent use of completely controlled mechanical ventilation in contemporary intensive care practice. Many modern intensive care units preferentially use spontaneous modes of ventilation where possible, whereby patients initiate effort to trigger each ventilator-supported breath. However, controlled ventilation is still used in some

cases (e.g. when patients are paralysed to minimise intracranial pressure immediately following traumatic brain injury) and therefore the potential consequences of controlled ventilation are still relevant.

Observational studies in humans have similarly shown that longer periods of mechanical ventilation are associated with greater weaning difficulty(Epstein et al., 2002, De Jonghe et al., 2007, Hermans et al., 2010). While longer periods of ventilation may be due to the underlying pathology, it is possible that mechanical ventilation further compounds respiratory muscle weakness in these patients, contributing to delayed weaning. Even following successful weaning, prolonged mechanical ventilation appears to affect respiratory muscle endurance. In a study of 20 patients who received mechanical ventilation for at least 24 hours(Chang et al., 2005a), there was a 12% reduction in endurance detectable approximately 1 week following weaning. Importantly, those ventilated for longer than 7 days showed significantly less fatigue resistance than those ventilated for fewer than 7 days. Furthermore, in a study of 116 patients ventilated longer than 7 days(De Jonghe et al., 2007), maximum inspiratory pressure (MIP) was found to be reduced and correlated with limb weakness. Although these studies do not provide any direct evidence of muscle atrophy, the results would be consistent with an atrophic response to mechanical ventilation.

Direct evidence for diaphragmatic atrophy with mechanical ventilation has been obtained in mechanically ventilated, brain-dead organ donors (Levine et al., 2008). Diaphragmatic biopsies from 14 brain-dead patients ventilated for between 18 and 69 hours were compared with biopsies from 8 surgical patients ventilated for no more than 3 hours. The biopsies from the brain-dead patients demonstrated statistically significant reductions in mean cross sectional area of both Type 1 and Type 2 muscle fibres, reduced glutathione and elevated levels of enzyme active caspase-3, suggesting increased proteolysis. These changes were not detectable in the control muscle studied for each patient (pectoralis major), suggesting that the atrophy and proteolysis observed was specific to the diaphragm and not a generalised phenomenon in skeletal muscle due to the abnormal physiology associated with brain death. As previously discussed, extrapolation of these results to mechanically ventilated patients whose ventilation has not been completely controlled should be done with caution. However, this study provides the most convincing evidence to date that mechanical ventilation has a direct adverse effect on the respiratory muscles(Tobin et al., 2010).

Muscle length-tension changes

The development of inspiratory muscle weakness with prolonged mechanical ventilation is likely to be compounded by other factors that impact on muscle performance. For example, positive end expiratory pressure (PEEP) is widely used as a therapeutic tool in patients with respiratory failure, but one of its effects is an adverse impact on the length-tension relationship of the diaphragm.

Like all skeletal muscles, the diaphragm's ability to generate force is related to the length of the muscle fibres(McCully and Faulkner, 1983). The implications of the diaphragm's length-tension relationship are well described in the literature pertaining to patients with COPD(Soicher J, 1998, McConnell and Romer, 2004a, Roussos, 1985). In this clinical group, chronic hyper-inflation, with average intrinsic PEEP of 2.4 cm H_2O (Dal Vecchio et al., 1990), results in adaptive shortening of the diaphragm causing a more flattened, less domed structure. This produces an adverse shift along the length-tension curve, so that diaphragmatic contraction generates less muscular force(McConnell and Romer, 2004a).

Mechanically ventilated patients are often prescribed relatively high levels of extrinsic PEEP (typically between 5 and 15 cm H_2O) as a mechanism to maintain alveolar recruitment, enhance oxygenation and counteract autoPEEP(Hess and Kacmarek, 2003). Unfortunately, this extrinsic PEEP may also lead to a flattening of the diaphragm and muscular shortening with disadvantageous shifts along the length-tension curve, further compounding inspiratory muscle weakness (as demonstrated in animal models(Torres et al., 1993)). Thus, in considering diaphragmatic weakness, the ideal prescription of mechanical ventilation should minimise PEEP wherever possible to reduce the negative impact on diaphragm strength. However, this must be balanced against the potential benefits of PEEP in patients with respiratory failure(Amato et al., 1998, Haitsma and Lachmann, 2006). Both impairment of the diaphragmatic length-tension relationship associated with excessive PEEP, and the worsening of respiratory mechanics seen with inadequate PEEP, may lead to an increase in respiratory drive and neuroventilatory efficiency(Passath et al., 2010). Recent work investigating the effects of PEEP in patients receiving Neurally Adjusted Ventilatory Assist confirms that increasing PEEP reduces respiratory drive, but also suggests that patients are able to adapt their neuroventilatory efficiency over a wide range of applied PEEP levels. In addition, it is possible to identify a

PEEP level at which breathing occurs with an optimum relationship between tidal volume and diaphragmatic electrical activity(Passath et al., 2010).

While the effects of mechanical ventilation on the diaphragm are relatively well-studied, the only available evidence regarding the effects of mechanical ventilation and PEEP on the performance of other inspiratory muscles, such as the parasternal intercostals, comes from animal research where positive pressure ventilation has been found to reduce intercostal force generation. However, it has been suggested that this force reduction may be due to rib orientation changes rather than muscular shortening (De Troyer and Wilson, 2009). In ventilator-dependent patients, the relative contribution of intercostal muscle dysfunction to inspiratory muscle weakness remains to be determined.

It has been suggested that when patients fail a spontaneous breathing trial, they typically exhibit rapid shallow breathing which causes a degree of dynamic hyperinflation (Tobin et al., 2010). As previously discussed, this hyperinflation will impair the length-tension relationship of the diaphragm and thus compromise inspiratory muscle strength(Tobin et al., 1998). Furthermore, both intrinsic PEEP and dynamic hyperinflation have been demonstrated in ventilator-dependent patients when they are removed from ventilatory support (Zakynthinos et al., 1995), indicating the presence of a high residual inspiratory load. It is yet to be established whether this intrinsic PEEP remains following successful weaning from ventilation.

Thus it is important to consider the possibility that the presence of intrinsic or either inadequate or excessive extrinsic PEEP may be contributing to impaired inspiratory muscle performance and apparent inspiratory muscle weakness.

Muscle weakness and failure to wean

Studies of patients who fail to wean from ventilation have been performed to determine whether there are physiological characteristics which distinguish those who wean from those who fail to wean. A small (n =10) prospective cohort study of ventilator-dependent patients found that those who could be weaned had significantly higher maximum inspiratory pressures (MIP) (mean 40 cm H_2O) than those who failed (mean 20 cm H_2O) (Epstein et al., 2002). Similar results were found in a second prospective cohort study of 30 patients who had failed initial weaning attempts in a weaning centre(Carlucci et al., 2009). In this study, an invasive device at the tip of the tracheostomy tube was used to

measure transdiaphragmatic pressures during spontaneous breathing trials (SBT). Patients who consistently failed these SBT concurrently demonstrated lower diaphragmatic pressures than those who weaned successfully, while those who successfully weaned demonstrated significantly higher MIP (mean 57 compared to mean 38 cm H_2O in success and failure groups respectively). The authors concluded that recovery of inspiratory muscle force may be a critical determinant of weaning success in this slow-to-wean population.

A larger prospective cohort study (n = 116) of patients ventilated for 7 days or longer(De Jonghe et al., 2007) found that not only was MIP significantly reduced in this group (mean 30 cm H_2O), but a low MIP was an independent predictor of delayed weaning. Yet paradoxically, other researchers have failed to demonstrate that measures of inspiratory muscle strength (e.g. MIP or negative inspiratory force) predict accurately weaning success or failure in the acute setting(Conti et al., 2004, Meade et al., 2001). For example, in a prospective blinded study of 93 patients, neither the MIP values, nor any other parameter investigated, had sufficient predictive power to distinguish between those who would wean successfully and those who would fail(Conti et al., 2004). Although inspiratory muscle weakness is a problem for patients undergoing prolonged ventilation, it may be that measures of inspiratory muscle strength only weakly reflect the overall complexity of respiratory dysfunction (and hence readiness to wean) and cannot be considered in isolation.

Implications of inspiratory muscle changes with mechanical ventilation

The available evidence strongly suggests that even relatively short durations of mechanical ventilation result in diaphragmatic atrophy, with associated abnormally high proteolysis. In healthy people, it is well established that high-resistance strengthening exercise causes both muscle anabolism and catabolism in skeletal muscle, with a net anabolic effect(Tipton and Ferrando, 2008). Resultant intra-muscular remodeling and gains in muscle cross-sectional area have been demonstrated in healthy participants following a 3-week high resistance training program(Seynnes et al., 2007). Therefore it is plausible that inspiratory muscle training could reverse or ameliorate inspiratory muscle proteolysis in ventilator-dependent patients, by providing a net anabolic stimulus. The associated inspiratory muscle strength gains could thus enhance weaning. However, appealing as this hypothesis may be, it remains unclear whether the respiratory muscle weakness associated with prolonged mechanical ventilation is reversible. In addition,

numerous other factors may contribute to muscle atrophy and apparent weakness in ventilator-dependent patients, which also must be considered.

Polyneuropathy

ICU-acquired weakness (ICUAW) is the current term used to describe the pathophysiological weakness observed in many critically ill patients, and while definitions and diagnostic guidelines have recently been clarified(Stevens et al., 2009), interpretation of data currently available in this area is clouded by the variations in definitions and terminology used prior to this (e.g. critical illness neuromyopathy, critical illness polyneuropathy). Critical illness polyneuropathy (CIP), a subset of ICUAW, is frequently present in critically ill patients but remains relatively under-diagnosed(Pandit and Agrawal, 2006). CIP has long been considered a contributor to difficulty in weaning from mechanical ventilation(Hund, 1999) and in an observational study of 21 patients with 'inability to wean'(Spitzer et al., 1992), 62% were found to have neuromuscular disease severe enough to account for ventilator dependence. A subsequent study of 40 patients ventilated for 5 days or longer (Maher et al., 1995) found that 83% had polyneuropathy, with a correlation between the severity of the polyneuropathy and weaning duration. In addition, while 25% of patients had reduced central drive, 15% had a combination of disorders. Thus any apparent muscle weakness in critically ill patients may be due to neuropathic as well as myopathic factors.

It has been suggested that as CIP is associated with duration of mechanical ventilation, then measures taken to reduce the period of ventilator-dependence may lessen the potential impact of CIP(Pandit and Agrawal, 2006). This association is confounded by the likelihood that severity of illness will contribute to both duration of mechanical ventilation and the development of CIP. A recent systematic review has observed that the respiratory muscles in patients with ICU-acquired weakness may be relatively spared the negative effects observed in peripheral muscles, possibly due to the intermittent stretch provided by the ventilator(Prentice et al., 2010). However, it is also possible that CIP is a contributor to ventilator dependence, rather than a consequence of it, and while the possible mechanisms for this remain unclear, lack of core stability due to weakness of structural trunk muscles may adversely impact respiratory function. In the absence of data, it is reasonable to consider CIP as a potential factor contributing to respiratory muscle dysfunction in ventilator-dependent patients.

In addition to ICUAW, pathologies of the peripheral neurological or neuromuscular systems, including Myasthenia Gravis and Guillain-Barre syndrome, frequently result in long-term ventilator-dependence and these underlying pathologies will almost certainly contribute to respiratory dysfunction. There is some limited evidence that inspiratory muscle training may increase inspiratory muscle strength and endurance in non-ventilated patients with myasthenia gravis(Fregonezi et al., 2005).

Further investigation of the interaction between peripheral neuromuscular disease and muscle retraining would be helpful. In the interim, the possible impact of muscle training on the pathophysiological processes involved in ICUAW must be considered.

Pharmacological effects

The potential effects of pharmacological agents on respiratory muscle strength also must be considered in critically ill patients. Neuromuscular blocking agents (NMBAs) and corticosteroids have both been implicated in the development of ICU acquired weakness(Schweickert and Hall, 2007). Although use has declined in recent years, NMBAs are still commonly used in the critical care environment, for management of both intracranial hypertension and ventilator dyssynchrony. It has been suggested that blockade of normal neuromuscular transmission and interference with endplate structure leads to an acceleration of critical illness myopathy; and that muscle will not recover until normal functional stimulation is provided(Wagenmakers, 2001).

Corticosteroids are prescribed for a diverse range of indications in the critically ill(Confalonieri and Meduri, 2011, Mason et al., 2009, van de Beek and de Gans, 2004), however the effect of corticosteroids on inspiratory muscle function in ventilator-dependent patients has not been studied in detail. In patients without underlying lung disease, extended duration high dose steroids (prednisone 1 to 1.5 mg/kg/day for 8 weeks) have been shown to reduce inspiratory muscle strength and endurance(Weiner et al., 1993). Interestingly, these reductions were reversed when corticosteroid doses were tapered. A subsequent study(Weiner et al., 1995) found that inspiratory muscle training prevented these negative effects of corticosteroid therapy. In contrast, no impact on inspiratory muscle strength was demonstrated in a study of moderate doses of corticosteroids (20mg daily) in 16 healthy participants(Wang et al., 1991). In asthmatic patients, the combination of corticosteroids and NMBAs may lead to profound and prolonged ICU acquired

weakness(Douglass et al., 1992, Griffin et al., 1992). Again, the specific effects on respiratory muscles have not been well studied.

It is therefore possible that the administration of either NMBAs or corticosteroids could further compound respiratory muscle weakness in ventilator-dependent patients. The degree to which these changes can be ameliorated by inspiratory muscle training is yet to be investigated.

Nutrition

A comprehensive analysis of the nutritional requirements of ventilator-dependent patients is beyond the scope of this review. However, while overfeeding has been on the list of factors to be considered in the difficult to wean patient for many years(Hess and Kacmarek, 2003), inadequate nutrition may also contribute to weaning difficulty.

It must be acknowledged that there is wide variability in the nutritional requirements between and within patients across their intensive care admission(Griffiths and Bongers, 2005). Trauma, major surgery and short-term starvation are all known to reduce protein synthesis(Griffiths and Bongers, 2005) . Furthermore, sepsis impairs mitochondrial function in both respiratory and limb muscles(Fredriksson and Rooyackers, 2007). However, septic patients demonstrate a relative preservation of energy sources (adenosine triphosphate, creatine phosphate) in respiratory muscles(Fredriksson and Rooyackers, 2007). This could enhance the training potential of respiratory muscles relative to peripheral muscles.

In healthy people, timing and quality of nutrition (particularly amino acid availability) directly affects muscle synthesis pathways(Tipton and Ferrando, 2008). Thus it would seem reasonable to conclude that adequate nutrition, titrated to account for anabolic muscle development, is necessary for successful inspiratory muscle training in critically ill patients. Conversely, ventilator-dependent patients with inadequate nutrition, or poor baseline metabolic status, may have inadequate substrate availability to match protein synthetic demand, reducing the efficacy of muscle training. However, the determination of nutritional requirements in critical illness remains controversial. There is some limited data from the bed rest (aerospace) literature suggesting that overfeeding may be harmful, with increased inflammatory markers and accelerated muscle atrophy in participants who do not reduce caloric intake after the initiation of bed rest(Biolo et al., 2008). Congruent with this, a recent

study in critical illness found that permissive underfeeding (goal 60-70% of estimated nutritional requirements) resulted in lower hospital mortality compared to those fed with a goal of 100% of estimated requirements(Arabi et al., 2011). These results are consistent with previous evidence that feeding goals of 33-65% of estimated requirements resulted in significantly improved hospital mortality than goals of >66%.

Specific supplementation to augment muscle hypertrophy and overall physical performance in response to training has long been studied in the sports literature, with relatively little cross over work to clinical populations. With particular relevance to muscle weakness and potential training effects, creatine supplements have been shown to augment training effects in healthy participants(Volek et al., 2004, Vandenberghe et al., 1997). However a randomised trial of creatine supplementation in 100 patients with COPD undergoing pulmonary rehabilitation failed to find improvements in exercise capacity in the creatine group(Deacon et al., 2008). To date no studies of creatine supplementation have been performed in critically ill patients.

Thus the interaction between the potential training benefits of inspiratory muscle training and nutritional status is complex. In the absence of clear guidelines regarding overall nutrition goals, or specific supplementation, inspiratory muscle training should be conducted with an appreciation of the potential influence of nutritional factors on resistance training benefits.

Psychological factors

Psychological stress has been identified as a potential factor contributing to difficult ventilatory weaning(Ambrosino and Gabbrielli, 2010, McCartney and Boland, 1994), yet there is limited data describing the extent of this problem. In a descriptive study of patient experiences of ventilator-dependence (Gale and O'Shanick, 1985) reported experiences included perceived catastrophic loss of control, perceiving the ventilator as an extension of one’s self, a spectrum of attitudes from depressed passivity to an agitated fight for control, and a dislike or fear of change, particularly with regard to weaning. While it must be acknowledged that this research is relatively old (1985), from a time when ventilators were less synchronised with patient effort, the findings are consistent with more recent studies. A prospective cohort study of 250 ventilator-dependent patients found that 88% of patients described their experience of being intubated and ventilated as moderately to extremely stressful(Samuelson, 2011). A follow-up study of these patients focused on memories of

intensive care and revealed prominent themes of physical and emotional ventilator-related distress (e.g. feeling unable to breathe, fear and panic, anxiety). Thus psychological distress should not be underestimated in ventilator-dependent patients.

The relationship between psychological stress or anxiety and dyspnoea has not been studied in ventilated patients. However, extrapolation from sports psychology, and specifically the perception of exertion, may be useful here. In athletes it has been proposed that during exercise the perception of exertion is not linear, but rather is best understood as a highly complex system where physiological feedback (e.g. via mechanoreceptors and chemoreceptors) is analysed by a central controller which also considers variables such as time to endpoint (e.g. how long until the end of the race) and previous experience[34,35]. Thus the perception of exertion (and therefore dyspnoea) is conscious and potentially modulated by psychological variables(Edwards and Walker, 2009, Edwards et al., 2008). If a ventilator-dependent patient's experience of weaning is analogous to an athlete's exercise conditions (i.e. both characterised by high ventilatory workloads and limited by perceived exertion), anxiety or psychological stress may well modulate the overall perception of effort and manifest as increased dyspnoea.

Although the subjective perception of dyspnoea has not been well studied in ventilated patients, it could be argued that one of the key methods employed to measure or predict weaning failure (i.e. rapid shallow breathing index(Yang and Tobin, 1991)) may be in fact an attempt to objectively quantify the subjective experience of dyspnoea. If subjective dyspnoea, rather than ventilatory capacity or fatigue, is actually the limiting factor in the context of weaning failure, it is not surprising that physiological-level measurement tools have failed to predict weaning success with great accuracy(Conti et al., 2004, Meade et al., 2001). This is clearly an area requiring further research, but in the interim a possible role for psychological factors as determinants of ventilator-dependence should be considered.

Indications for inspiratory muscle training

In light of the above evidence regarding ventilator-dependent respiratory dysfunction, clinicians have been urged to minimise controlled ventilation and reduce the doses of drugs known to affect respiratory muscle function(Cader et al., 2010). These approaches may reduce inspiratory muscle dysfunction but are unlikely to completely avoid it; even with these strategies, respiratory muscle weakness remains detectable approximately 7

days following successful weaning(Chang et al., 2005a). As skeletal muscle weakness is generally a reversible phenomenon, it seems logical to employ training methods as early as possible to minimise the predictable effects of reduced inspiratory muscle work with mechanical ventilation. Furthermore, as prolonged mechanical ventilation is associated with poor functional outcomes (e.g. 21% complete functional dependency at 12 months(Unroe et al., 2010)), any intervention with the potential to hasten ventilatory weaning, or avoid long-term ventilator dependence, deserves consideration.

MECHANISM OF INSPIRATORY MUSCLE TRAINING

Definition of inspiratory muscle training

Inspiratory muscle training uses progressive resistance to provide loading to the inspiratory muscles to achieve a strengthening effect. Inspiratory muscle training devices have evolved considerably and now most commonly consist of a commercially available spring-loaded threshold valve which can be easily adjusted to provide incremental resistance. Importantly, the threshold design requires a specified pressure-level to be achieved with each breath, regardless of flow-rate, allowing the intensity of resistance to be titrated and progressed accurately. In non-ventilated patients this device is used with a mouthpiece and nose clip, but for ventilator-dependent patients it can be attached directly to the tracheostomy or endotracheal tube via a simple connector while patients are briefly removed from ventilatory support.

Mechanisms of improvement with inspiratory muscle training

The evidence explaining possible mechanisms of change can be grouped into 4 categories: adaptations in muscle structure, changes in muscle perfusion and metabolism, neural adaptations and modulation of dyspnoea. Each of these will be described in detail with specific reference to inspiratory muscle training.

Muscle structure and fibre type

There is some direct evidence for the effect of inspiratory muscle training on muscle structure and specifically muscle fibre type. One key randomised trial (Ramirez-Sarmiento et al., 2002) investigated the effects of inspiratory muscle training in patients with chronic obstructive pulmonary disease by taking biopsies of both the external intercostal muscles and the vastus lateralis muscle (control) before and after an inspiratory muscle training program. These researchers found that training for 30 minutes, 5 days a week for 5 weeks

at 40-50% of maximal inspiratory pressure (MIP) resulted in increases in both Type 1 (38%) and Type 2 fibres (21%), whereas no changes were detected in the control muscle. This study was the first to provide clear evidence of muscular adaptation in response to a loading stimulus, but given the load was relatively low (40 – 50% of MIP) and subsequent training regimes in the literature have tended towards higher training intensities (e.g. 45% - 101% of baseline MIP)(Hill et al., 2006), the full potential of muscle fibre adaptation in response to inspiratory muscle training remains to be elucidated.

In the aforementioned study, inspiratory muscle training resulted in proliferation of both fibre types but Type 1 to a greater extent. Patients with chronic obstructive pulmonary disease have an abnormally high ratio of Type 1 to Type 2 fibres in the diaphragm(Levine et al., 2003). It is yet to be determined whether it is the inspiratory muscle training that preferentially increased Type 1 fibres in relation to Type 2, or whether this is solely a reflection of the underlying pathology of chronic obstructive pulmonary disease in this particular study.

There is corroborative evidence that inspiratory muscle training increases proliferation of muscle fibres in healthy people. A randomised trial of 20 participants who performed inspiratory muscle training at 80% of MIP for 8 weeks found not just increases in MIP and exercise capacity, but also in diaphragm thickness in the treatment group(Enright et al., 2006). Similarly a smaller randomised trial of healthy participants reported an 8 – 12% increase in diaphragm thickness in response to 4 weeks of inspiratory muscle training at 50% of MIP(Downey et al., 2007). Thus proliferation of inspiratory muscle fibres in response to inspiratory muscle training is neither unique to patients with chronic obstructive pulmonary disease, nor to the external intercostal muscles alone. Accordingly, muscle fibre proliferation may be considered a key mechanism of improvement attributable to inspiratory muscle training.

Enhanced muscle perfusion, metabolism and reduced lactate production

There is evidence that inspiratory muscle training enhances muscle metabolism by affecting the sensitivity of a fatigue-induced metaboreflex (Figure 1). In healthy humans, inspiratory muscle work during maximal exercise is inversely related to limb muscle perfusion(Harms et al., 1997) and it has been suggested that this is due to a sympathetically mediated metaboreflex which preferentially redistributes blood flow away

from exercising limb muscles in order to return blood supply to the fatiguing inspiratory muscles (Harms et al., 1997, Witt et al., 2007, Romer and Polkey, 2008).

In 2006, a small study of 8 healthy participants (McConnell and Lomax, 2006) demonstrated that fatigue of the inspiratory muscles hastened fatigue of the plantar flexors, but inspiratory muscle training abolished this effect. These authors speculated that this reduced fatigue of peripheral muscles following inspiratory muscle training, possibly as a result of decreased or delayed responsiveness of the metaboreflex, may partially explain improvement in exercise tolerance reported as a benefit of inspiratory muscle training.

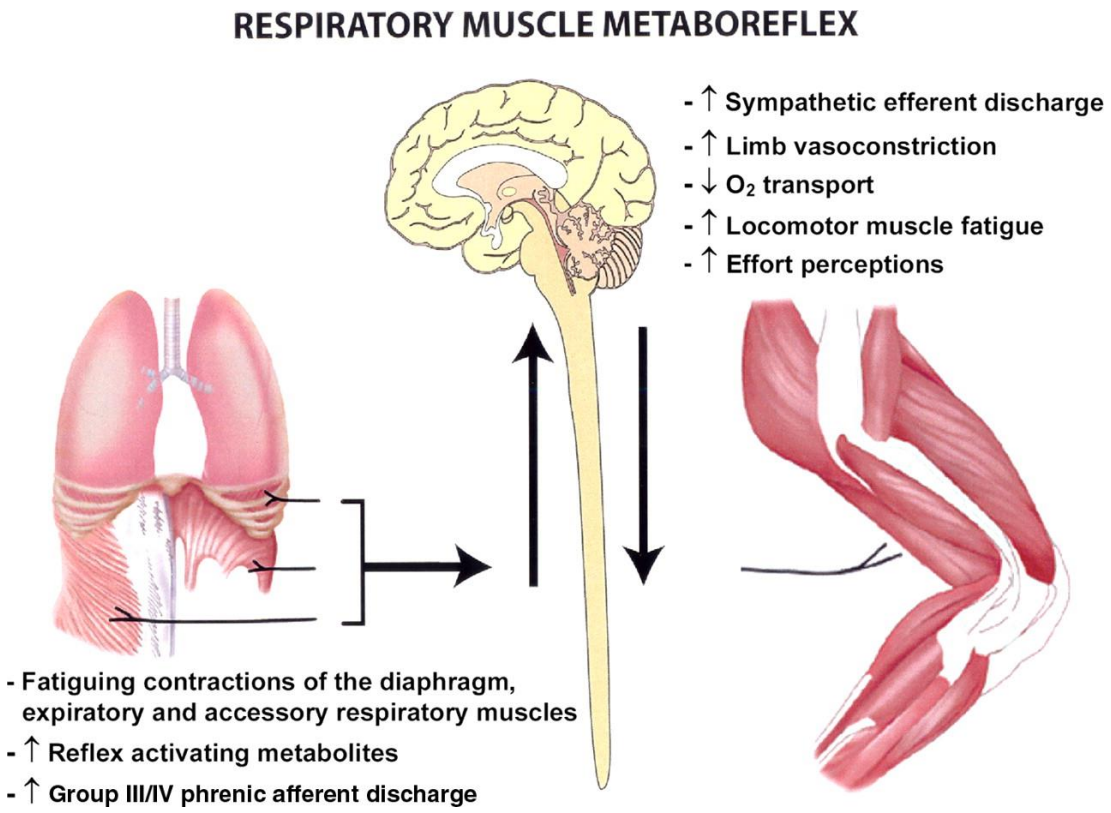


Figure 1: Respiratory muscle metaboreflex.

From Romer & Polkey (2008). Journal of Applied Physiology 104 (3), 879-888.

A subsequent randomised trial of 16 healthy participants (Witt et al., 2007) specifically analysed the effect of inspiratory muscle training on the metaboreflex as measured by changes in heart rate and blood pressure. These authors confirmed that inspiratory muscle training attenuates the metaboreflex response during fatiguing respiratory work, describing a blunted sympathetic response (i.e. significantly lower heart rate and blood pressures measured in the training group during fatiguing inspiration). These authors suggested that

the blunted sympathetic response could be a result of decreased sensitivity to lactic acid produced during fatiguing work, or alternatively an increased aerobic capacity which leads to lower levels of lactate production.

A more detailed analysis of aerobic pathways in 16 healthy participants(Bailey et al., 2010) found that inspiratory muscle training resulted in improved VO_2 dynamics, specifically the slow component amplitude, as well as reduced dyspnoea and increased exercise tolerance. These authors attributed this improved aerobic capacity to the enhanced blood flow in the exercising limbs as a result of a reduced metaboreflex.

Following an early observational study that suggested inspiratory muscle training reduces lactate levels (Spengler et al., 1999), the relationship between inspiratory muscle training and lactate has been clarified. In a randomised trial of 22 healthy participants (Brown et al., 2008), inspiratory muscle training resulted in significantly lower blood lactate levels in the treatment group during a high intensity voluntary hyperpnoea task. These results indicate that the inspiratory muscles themselves are a significant source of the blood lactate levels detected during fatiguing inspiratory workloads. This is consistent with previous studies showing that inspiratory muscle training reduces lactate levels during treadmill running in competitive athletes (Leddy et al., 2007) as well as during cycling in healthy untrained people (McConnell and Sharpe, 2005).

Together, this evidence suggests that inspiratory muscle training enhances overall aerobic capacity by not just reducing lactate production in the inspiratory muscles themselves (possibly due to an increased ratio of Type 1 muscle fibres), but also by enhancing blood flow to peripheral muscles by attenuating the metaboreflex that would otherwise ‘steal’ blood flow and redirect it to fatiguing respiratory muscles during high intensity exercise. This overall enhancement of aerobic capacity may explain the global improvements in exercise performance described as a result of inspiratory muscle training in both healthy people and those with underlying pathology.

Neural adaptations

It is well accepted that the strength gains observed with skeletal muscle training are at least partly attributable to neural mechanisms, particularly early in the training phase where increases in strength precede changes in muscle mass (Enoka, 1997, Gabriel et al., 2006). Using magnetic resonance imaging it has been shown with quadriceps training, less muscle is required to lift the same load and strength gains are also apparent in a contralateral untrained muscle (Ploutz et al., 1994). Furthermore, strength gains associated with mental practice alone can be attributed to neural changes in the absence of muscle-level changes (Yue and Cole, 1992). Possible elements of neural adaptation include enhanced synchronisation of motor unit firing, decreased co-activation of antagonistic muscles, increased reflex potentiation and more efficient motor programming as manifested by reduced motor drive (Kellerman et al., 2000, Enoka, 1997, Yue and Cole, 1992, Gabriel et al., 2006).

There are 2 studies which specifically investigate the neural adaptations that occur with inspiratory muscle training. The first (Huang et al., 2003) measured the effect of inspiratory muscle training on inspiratory motor drive in 23 healthy participants who underwent inspiratory muscle training 5 days a week, training at 75% of MIP. After 4 weeks of training, which resulted in a 36% increase in MIP, there was a 22% decrease in inspiratory motor drive when measured as mouth occlusion pressure. Moreover there was a significant negative correlation between MIP and motor drive. These results suggest that inspiratory muscle training causes a down-regulation in motor programming, reflecting less drive required for a given respiratory workload.

The second study (Ross et al., 2007) measured the effect of inspiratory muscle training on the peripheral and corticospinal excitability of the diaphragm in 10 healthy participants. Following submaximal loads (40% MIP, 2 sets of 30 breaths), there was an increase in neuromuscular junction and muscle membrane propagation indicating increased peripheral excitability. Conversely there was a reduction in diaphragmatic excitability at the corticospinal level, possibly indicating better neuronal synchronisation, increased motor unit firing or more efficient programming. However within 15 minutes of cessation of inspiratory muscle training these changes in excitability were no longer detectable. The benefit of transient changes in neural excitability remains unclear, but may be relevant to specific treatment scenarios (e.g. immediately prior to extubation for ventilated patients, or

immediately prior to a race for an elite athlete). Nonetheless, this study provides further evidence that inspiratory muscle training causes neural adaptations at multiple levels.

Given that some inspiratory muscle training studies have reported strength gains within the first 2 weeks of training (Johnson et al., 2007), and it is generally accepted that structural changes in the muscle are unlikely before approximately 8 weeks of strengthening (Gabriel et al., 2006), it seems highly likely that neural adaptations are a critical element of the training effect of inspiratory muscle training particularly in the first few weeks.

Modulation of dyspnoea

Evidence regarding purely physiological explanations of fatigue and dyspnoea have been recently challenged (Edwards and Walker, 2009). A randomised trial of 16 healthy participants (Edwards et al., 2008) compared concurrent inspiratory muscle training and running training with running alone (control). Within 4 weeks of training, there was no significant difference between inspiratory muscle training and control groups in terms of MIP, whereas there were significant between-group differences in both exercise performance (5000 km running) and related dyspnoea (RPE scores during running). These results suggest that, at least in the first few weeks of inspiratory muscle training, strength gains are much less important than changes in the perception of breathing effort in determining exercise performance.

The authors of this study argue that respiratory muscle receptor feedback is only one of a complex web of factors (both physiological and psychological) which are processed centrally to derive an overall perception of dyspnoea. Insofar as exercise performance is limited by dyspnoea, inspiratory muscle training could well play a role in desensitising the conscious mind to the effort associated with high respiratory workloads and in doing so allow the athlete to achieve greater performance. This hypothesis, although in its infancy, sits neatly with the evidence of improvement noted with inspiratory muscle training in patients with chronic obstructive pulmonary disease, where dyspnoea is often a critical determinant of independence and quality of life (Hill et al., 2004). Such modulation of dyspnoea may also be highly relevant to intensive care patients during the weaning process. Future research into the mechanisms of improvement noted with inspiratory muscle training should not underestimate psychological dimensions.

Summary of mechanisms of improvement with inspiratory muscle training

While the precise mechanisms of improvement produced by inspiratory muscle training are not yet fully understood, there is reasonable evidence that inspiratory muscle training increases the proliferation of inspiratory muscle fibres; reduces blood lactate production and the impact of the sympathetically-mediated metaboreflex, allowing enhanced blood flow to peripheral muscles; and increases the efficiency of motor programming and / or peripheral neural networks as reflected by reduced motor outflow for a given inspiratory workload. In general, changes in the first few weeks of inspiratory muscle training are likely to be related to neural adaptations and central modulations of the perception of dyspnoea, whereas later improvements may also be attributable to structural and metabolic changes. These changes help to explain not just the improvement in inspiratory muscle strength observed with inspiratory muscle training, but also the enhancement of exercise performance that has been reported in both healthy people and those with underlying pathophysiology.

EFFICACY OF INSPIRATORY MUSCLE TRAINING IN OTHER POPULATIONS

Inspiratory muscle training has evolved considerably over the past 35 years, with proliferation of evidence supporting its efficacy in both chronic obstructive pulmonary disease and athletes. Whilst these two groups boast the majority of published research on inspiratory muscle training, there has also been a gradual emergence of evidence for the efficacy of inspiratory muscle training in a broad range of other patient groups. This review summarises the evidence to date for the efficacy of inspiratory muscle training in both patients with chronic obstructive pulmonary disease and athletes. For a detailed discussion of the evidence for inspiratory muscle training in other patient groups in the context of the wider literature, please refer to Appendix A.

The effects of inspiratory muscle training in chronic obstructive pulmonary disease

Since 1991, a series of systematic reviews and meta-analyses of the effects of inspiratory muscle training in chronic obstructive pulmonary disease have shown dramatically different results (see Table 1). Whereas the first review in 1991(Smith et al., 1992) revealed no significant effects of inspiratory muscle training, the major limitation of this review was the inclusion of many studies which failed to control for the intensity of the resistance provided during inspiratory muscle training (e.g. by using non-linear resistors for training, in which the intensity of the resistance is flow-dependent and can therefore be manipulated by the patient's pattern of breathing)(Belman et al., 1994). By 1997 limited

evidence emerged that training at 30% of MIP resulted in improved inspiratory strength, endurance, dyspnoea and exercise tolerance, whereas training at 10 – 17% of MIP either did not result in any change (Lisboa et al., 1994) or resulted in small increases in inspiratory strength only (Lisboa et al., 1997). When Lotters and colleagues (Lotters et al., 2002) subsequently reviewed studies where the training intensity was a minimum of 30% of MIP, a very different picture emerged: inspiratory muscle training resulted in significant improvements in inspiratory muscle strength and endurance, as well as reduction in dyspnoea; however no significant effect of inspiratory muscle training on exercise tolerance could be detected. Nonetheless Lotters and colleagues suggested that inspiratory muscle training may be a useful addition to pulmonary rehabilitation programs for patients with known inspiratory muscle weakness.

Table 1: Outcomes of inspiratory muscle training in chronic obstructive pulmonary disease from systematic reviews

Systematic Review /Meta-analysis	Inspiratory muscle strength	Inspiratory muscle endurance	Dyspnoea	Exercise tolerance	Quality of life
Smith et al. (1992)	X	X	N/A	X	N/A
Lotters et al. (2002)	✓	✓	✓	X	N/A
Geddes et al. (2005) & update Geddes et al. (2008)	✓	✓	✓	✓	X
Crowe et al. (2005)	✓	✓	✓*	✓*	✓*
Shoemaker et al. (2009)	✓	✓	✓	✓	✓

* = compared to education only; results equivocal comparing inspiratory muscle training to exercise; ✓ = significant at $p<0.05$

As the number and quality of trials investigating the effects of inspiratory muscle training increased, further evidence mounted regarding exercise tolerance and quality of life in this patient group. In the meta-analysis performed by Geddes et al (2005), significant effects for increased exercise capacity could be detected, while Crowe et al (2005) similarly reported benefits for both exercise tolerance and quality of life when comparing inspiratory muscle training to education programs. Most recently, Shoemaker and colleagues (2009) reported significant effects for inspiratory muscle training for not just inspiratory muscle strength, endurance and dyspnoea, but also health related quality of life and exercise tolerance when measured using walking tests.

Whether or not inspiratory muscle training offers additional benefits to a standard whole body pulmonary rehabilitation program for patients with chronic obstructive pulmonary disease remains controversial. In a randomised trial, Magadle and colleagues (2007) found inspiratory muscle training conveyed additional benefits (increased MIP, reduced dyspnoea and increased health-related quality of life) beyond those detected following pulmonary rehabilitation alone. However, a subsequent systematic review by O'Brien et al (O'Brien et al., 2008) comparing combined inspiratory muscle training and exercise with exercise alone did not detect any significant outcome for quality of life, despite finding increase inspiratory muscle strength and one significant measure of improved exercise tolerance in the training group. This suggests that further studies are required to determine if the addition of inspiratory muscle training to pulmonary rehabilitation results in clinically significant outcomes beyond improving muscle strength alone.

Few studies have assessed the long-term impact of inspiratory muscle training in patients with chronic obstructive pulmonary disease. One study of 38 patients (Weiner et al., 2004) trained patients with inspiratory muscle training at 60% MIP for 30 minutes 6 days a week for 3 months. Following the initial 3 month program, patients were randomised to either a maintenance program (same intensity and duration but only 3 sessions per week) or a sham comparison (minimal load at same intensity, frequency and duration) for another 12 months. While this study was hampered by high drop-out rates (7 from the control group, 4 from inspiratory muscle training group), the results indicated that without a maintenance program, the benefits of the initial inspiratory muscle training program progressively declined to baseline levels over 1 year. A subsequent long-term randomised trial (Beckerman et al., 2005) compared inspiratory muscle training and sham training at 3, 6, 9 and 12 months. While the improved MIP and exercise tolerance at 3 months were predictable, somewhat more impressive was a reduction in hospitalisation days by 30% in the inspiratory muscle training group across the one year period. Furthermore, significant quality of life differences in favour of the training group were not detectable until 6 months, but these were then maintained until 12 months. Surprisingly, changes in dyspnoea were not detectable until 9 months but were in favour of the training group. Care must be taken interpreting the results of this study due to the high drop-out rate (11 of 42) and low attendance rates reported. However these results do suggest that the effects of long-term inspiratory muscle training in these patients warrant further investigation.

As inspiratory muscle training intensity has increased and training methods have become more standardised (i.e. by using pressure threshold devices as opposed to more variable equipment), the effects of inspiratory muscle training have become clearer for patients with chronic obstructive pulmonary disease. It is now well accepted that inspiratory muscle training is a useful and feasible treatment option for these patients and guidelines for clinicians are now available (Hill et al., 2010). The actual pattern of usage of inspiratory muscle training by physiotherapists is yet to be determined.

The effects of inspiratory muscle training in athletes and healthy people

Respiratory muscle training in healthy people has been reported in the literature since 1976 (Leith and Bradley, 1976). The potential of inspiratory muscle training to enhance athletic performance has fuelled much research, particularly in the endurance disciplines of rowing, cycling, running and swimming, all of which may be limited by respiratory muscle capacity. There is substantial evidence that inspiratory muscle training increases inspiratory muscle strength in healthy or athletic people (Table 2). It is less clear how these changes occur or how increased strength translates into enhanced exercise performance. However, like patients with chronic obstructive pulmonary disease, athletes' perception of dyspnoea may be a critical limiting factor for exercise tolerance.

Considering the importance of intensity described for patients with chronic obstructive pulmonary disease, it is interesting that the intensity of resistance featured in all training programs in Table 2 is a minimum of 50% of MIP. While the duration of training programs studied ranges from 4 to 11 weeks, the largest changes in MIP were typically detected within the first 4 to 6 weeks of training (Volianitis et al., 2001, Klusiewicz et al., 2008) and in some studies, as early as 2 weeks (Johnson et al., 2007, Downey et al., 2007). One particularly well-designed study (Gething et al., 2004b), with both sham and control groups, further demonstrated that the improvements in MIP were not due to familiarisation or placebo effects. Most studies did not follow up patients beyond the training period, but one study of elite rowers (Klusiewicz et al., 2008) showed that at 14 weeks post training cessation, MIP remained higher than baseline measurements.

Table 2: Changes in inspiratory muscle strength in healthy participants and trained athletes

Randomised Trial	Sport / Healthy Participants	Intensity (%MIP)	Duration (wk)	Frequency (sessions/wk)	△MIP*
Volianitis et al. (2001)	Rowing	50%	11	14	↑ 45%
Klusiewicz et al. (2008)	Rowing	62-77%	11	14	↑ 34%
Riganas et al. (2008)	Rowing	80%	6	7	↑ 28%
Gething et al. (2004b)	Cycling	80%	10	3	↑ 34%
Johnson et al. (2007)	Cycling	50%	6	14	↑ 17%
Sonetti et al. (2001)	Cycling	50%	5	5	↑ 8%
Kilding et al. (2010)	Swimming	50%	6	14	↑ 9%
Williams et al. (2002)	Running	50-65%	4	4 – 5	↑ 31%
Inbar et al. (2000)	Mixed	80%	10	6	↑25%
McConnell and Sharpe (2005)	Healthy	50%	6	14	↑26%
Enright et al. (2006)	Healthy	80%	8	3	↑ 41%
Downey et al. (2007)	Healthy	50%	4	10	↑ 24%
Bailey et al. (2010)	Healthy	50%	4	14	↑ 17%

* = significant at $p<0.05$, MIP = maximum inspiratory pressure

Increased MIP was frequently associated with improved exercise performance (Volianitis et al., 2001, Gething et al., 2004b, Johnson et al., 2007, Enright et al., 2006, Bailey et al., 2010, Leddy et al., 2007), although not directly correlated to it(Johnson et al., 2007, Bailey et al., 2010) suggesting that MIP is not necessarily a good predictor of exercise capacity. The magnitude of the improvements detected were not necessarily large (e.g. 1.5% reduction in 100 m swim time (Kilding et al., 2010); 2.66% improvement in 25 km cycling time trial (Johnson et al., 2007), 4% improvement in 4 mile run time (Leddy et al., 2007)) however as suggested by Voliantis and colleagues (2001) performance improvements smaller than 2% may be important in determining victory in elite sporting events and thus remain of practical significance. In the few studies where exercise performance was not enhanced by inspiratory muscle training, these results can be explained by potentially conflicting training strategies such as concurrent inspiratory and expiratory muscle training (Wells et al., 2005); flawed sham devices that could potentially provide a training stimulus (Sonetti et al., 2001, Goosey-Tolfrey et al., 2010); poor adherence to the training regimen(Goosey-Tolfrey et al., 2010); or small sample sizes resulting in inadequate statistical power (McConnell and Romer, 2004b, Williams et al., 2002, Riganas et al., 2008).

Fatigue resistance appears to be enhanced following inspiratory muscle training in athletic and normal healthy people (Volianitis et al., 2001, Bailey et al., 2010). In one study of trained runners (Leddy et al., 2007) a period of rest (7 days) following cessation of the inspiratory muscle training program revealed more pronounced improvements in endurance when compared to measurement 1 day following program cessation. Inspiratory muscle training has also been shown to accelerate recovery from endurance events in trained cyclists (Romer et al., 2002).

It is worth highlighting one randomised trial (Edwards et al., 2008) which compared concurrent running training and inspiratory muscle training with running alone (control). This study failed to show differences between inspiratory muscle training and control groups in MIP (both increased significantly). It is possible that the running training alone was sufficient training stimulus to increase MIP in the control group, meaning the short inspiratory muscle training period (4 weeks) was inadequate to produce a significant between-group change in MIP. However this study did demonstrate significantly enhanced 5000 m running performance in the inspiratory muscle training group (4.3% compared to 2.2% in the control) and significantly reduced RPE during week 4 of running training in the inspiratory muscle training group alone. These authors have suggested that central modulation of dyspnoea may be a critical effect of inspiratory muscle training in terms of enhanced exercise performance.

Inspiratory muscle training in athletes results in lower levels of dyspnoea (Bailey et al., 2010, Gething et al., 2004a, Kilding et al., 2010) and more specifically in a reduced estimation of the magnitude of a respiratory load (Kellerman et al., 2000). These findings further indicate that inspiratory muscle training's effect on dyspnoea may be a critical determinant of exercise performance success in athletes.

INSPIRATORY MUSCLE TRAINING IN OTHER POPULATIONS

The efficacy of inspiratory muscle training has been explored in other patient groups. For a detailed summary of this literature, please refer to Appendix A.

INSPIRATORY MUSCLE TRAINING IN VENTILATOR-DEPENDENT PATIENTS

Evidence for inspiratory muscle training in ventilator-dependent patients

Despite some promising early case studies of inspiratory muscle training in ventilated patients (Sprague and Hopkins, 2003, Martin et al., 2002, Bissett and Leditschke, 2007), a single-centre randomised trial in 2005 concluded that inspiratory muscle training was ineffective this group (Caruso et al., 2005). However, this study used ventilator manipulations rather than a threshold device and had several limitations. Firstly, the inspiratory muscle training was performed at a relatively low intensity (i.e. 10 - 40% of maximum) which may not have provided an adequate training stimulus; secondly the low number of participants (n =25) may have rendered the study vulnerable to Type 2 errors; thirdly, despite attempts to optimise sedation levels, they reported less than ideal cooperation from some of their participants, whereas full alert cooperation is considered essential in other training protocols(Martin et al., 2002, Sprague and Hopkins, 2003, Bissett and Leditschke, 2007); and fourthly the equivalence of ventilator manipulations and threshold-device training may be challenged, not least because temporary removal from all ventilatory support may be an essential element of successful inspiratory muscle training. Based on these limitations, the conclusion that inspiratory muscle training is ineffective for ventilated patients was arguably premature.

In contrast two recent randomised trials, both providing inspiratory muscle training via a removable threshold device, demonstrated significant improvements in ventilated patients. In a study of 41 patients aged 70 or older, Cader and colleagues used 5-minute inspiratory muscle training sessions twice daily, commencing at 30% of MIP and increasing intensity by 10% daily(Cader et al., 2010). These researchers found a significant increase in inspiratory muscle strength (mean difference in MIP of 7.6 cm H_2O 95% CI 5.8 to 9.4), and a decrease in both the rapid shallow breathing index and weaning time, (mean difference 1.7 days, 95% CI 0.4 to 3.0). Subsequently, Martin et al(Martin et al., 2011) used high intensity interval training (highest tolerable resistance, progressed daily; sets of 6 to 10 breaths with rests on the ventilator in between) and found that inspiratory muscle training with a threshold device resulted in significant increases in inspiratory muscle strength (from mean 44.4 to 54.1 cm H_2O) whereas no such increase was observable in the control group. The treatment group had significantly more patients successfully weaned than the control group following 28 days of intervention (treatment group 71%, 95% CI 55% to 84%; sham group 47%, 95% CI = 31% to 63%). The number needed to treat for these effects was reported as 4 (95% CI 2 to 80). Despite quite different training strategies, both these

studies demonstrated that inspiratory muscle training results in increased inspiratory muscle strength and favourable weaning outcomes in ventilator-dependent patients. The optimal training parameters are yet to be established.

The mechanism of improvement with inspiratory muscle training in ventilated patients has not been investigated. The high-intensity training protocols used in both randomised trials described above may have provided an adequate training stimulus to halt or reverse the atrophy and proteolysis that occurs in patients undergoing mechanical ventilation (as described in Figure 2).

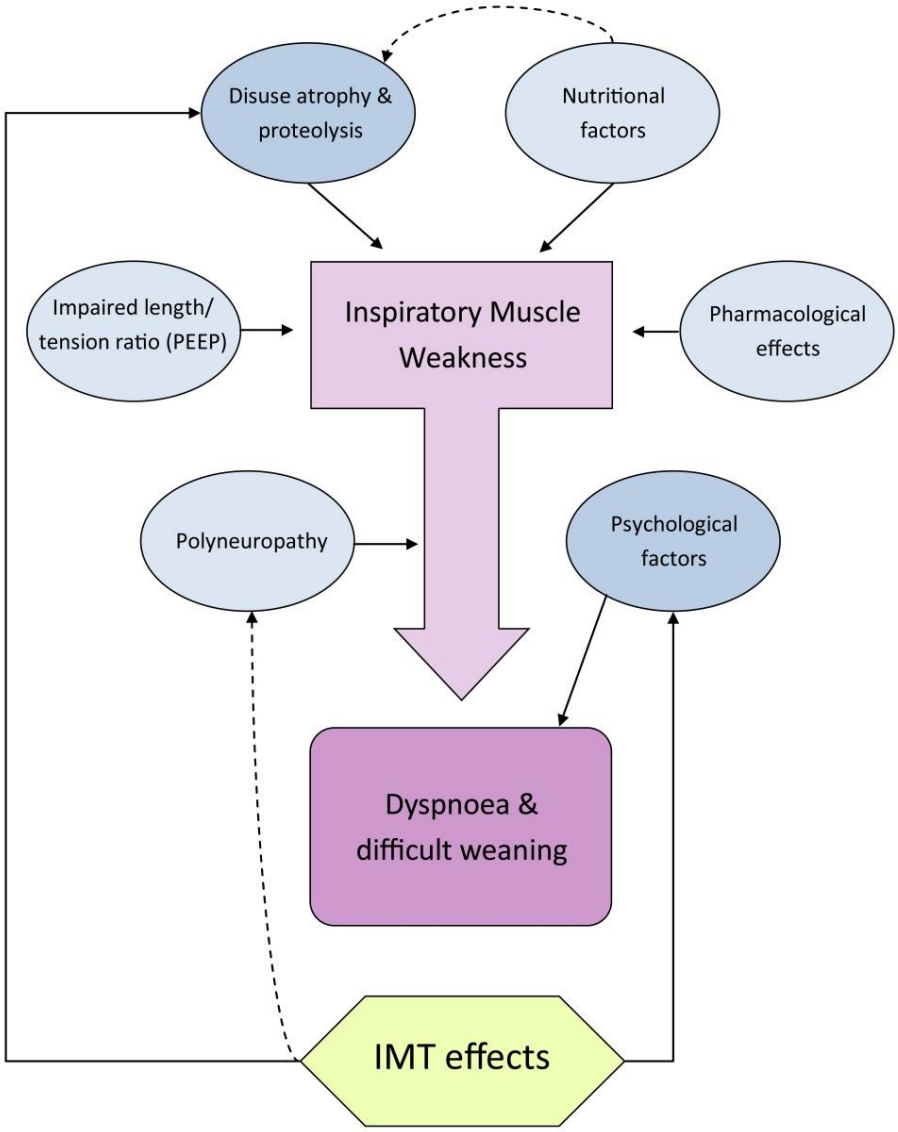


Figure 2: Model of inspiratory muscle training and enhanced weaning from mechanical ventilation

Inspiratory muscle training could also attenuate the metaboreflex pathways described previously, contributing to enhanced limb muscle perfusion, facilitating early mobilisation and thus accelerating recovery. Investigation of these hypotheses is warranted.

Psychological implications of inspiratory muscle training in ventilator-dependent patients

Why would inspiratory muscle training with a threshold device be effective in increasing strength and enhancing weaning when ventilator manipulations are not? As discussed above, the psychological aspects of ventilator-dependence can be significant. Threshold-based inspiratory muscle training protocols require patients to gradually develop confidence breathing unassisted (i.e. in short bursts off the ventilator whilst supervised and encouraged by a physiotherapist). This coached inspiratory muscle training approach may build patients' confidence breathing without ventilatory support, alleviate weaning-related anxiety, reduce the perception of effort and dyspnoea, and ultimately increase the likelihood of weaning success (see Figure 2). This would be consistent with evidence from the sports literature, where perception of effort is considered a critical determinant of performance improvements in the absence of physiological changes in response to inspiratory muscle training (Edwards et al., 2008).

Safety and feasibility of inspiratory muscle training in ventilator-dependent patients

The safety of threshold-based inspiratory muscle training in selected ventilator-dependent patients has been recently established with stable physiological parameters (blood pressure, heart rate, oxygen saturation and respiratory rate) in response to treatment and no adverse outcomes reported in an analysis of 195 treatment sessions (Bissett et al., 2012b) (see Chapter 2). This is corroborated by the two recent randomised trials, neither of which reported adverse outcomes in response to treatment (Cader et al., 2010, Martin et al., 2011), but contrasts with the study of inspiratory muscle training using ventilator manipulations(Caruso et al., 2005) which reported 23 cases (14%) of adverse physiological outcomes (i.e. desaturation, tachypnoea, haemodynamic instability and arrhythmia). Careful selection of stable, alert and cooperative patients who are able to psychologically tolerate the temporary high inspiratory workload of inspiratory muscle training should enhance feasibility and reduce potential tachypnoeic or tachycardic responses that could be panic-related.

There are limitations to the usage of inspiratory muscle training using a threshold device in ventilated patients: patients must be alert and able to cooperate with training, they must be medically stable and they must not be heavily reliant on high levels of ventilatory support (e.g. PEEP < 10 cm H_2O, FiO_2 < 60%)(Bissett et al., 2012b). Not all critically ill patients will be suitable for inspiratory muscle training, particularly in the most acute phase of their management. However any patient who is at risk of ventilator-induced respiratory dysfunction, particularly those whose mechanical ventilation has exceeded 7 days, should be screened for suitability for inspiratory muscle training. Minimising sedation is essential to maximise training opportunities and will enable the patient to fully participate in comprehensive early physical therapy, of which inspiratory muscle training could be an important element.

Summary of respiratory dysfunction and inspiratory muscle training for ventilator-dependent patients

In summary, mechanical ventilation results in respiratory dysfunction, with muscle atrophy, secondary to disuse proteolysis, and inspiratory muscle shortening due to high PEEP leading to impairment of inspiratory muscle force generation capacity. This weakness is likely to be further compounded by critical illness polyneuropathy, nutritional impairment and the administration of corticosteroids and neuromuscular blocking agents. Psychological distress and anxiety is also likely to contribute to ventilator-dependence and may hamper weaning efforts. Inspiratory muscle training improves inspiratory muscle strength and exercise performance in healthy and athletic people, as well as those with chronic disease. Early evidence suggests that inspiratory muscle training increases inspiratory muscle strength and reduces weaning times in ventilated patients, with enhanced weaning outcomes. Further research is required to elucidate the mechanisms of these improvements in ventilated patients, but these are likely to be related to enhanced protein synthesis, reduced dyspnoea and psychological readiness to tolerate high respiratory workloads.

Clearly not all ventilator-dependent patients are suitable for inspiratory muscle training. Nonetheless, given the costs of ventilator-dependence, for both the patient and the health care system (Ambrosino and Gabbrielli, 2010) clinicians could screen their patients for suitability for inspiratory muscle training and the evidence suggests many may benefit. Indeed, these studies provide further impetus for clinicians to maximise alertness in

intensive care patients to facilitate training. Further research is needed to determine the ideal training parameters, and also to establish whether physiological improvements (as reflected in improved inspiratory muscle strength) translate into meaningful improvements in patient-centred outcomes such as quality of life, exercise tolerance and functional performance (i.e. similar to the benefits observed with inspiratory muscle training in chronic lung disease and athletes). Nonetheless, if inspiratory muscle training can hasten ventilatory weaning by even one day, then these early studies suggest inspiratory muscle training may be a wise investment in the modern intensive care unit.

OUTLINE OF THE THESIS

This thesis comprises 5 studies that together describe the feasibility and efficacy of inspiratory muscle training in intensive care patients who have experienced a minimum of 7 days of invasive mechanical ventilation (
Figure 3).

In Study 1, the safety and feasibility of inspiratory muscle training in ventilator-dependent patients is described. In this study, physiological variables including oxygen saturation, blood pressure, heart rate and respiratory rate are reported before, during and after inspiratory muscle training sessions in intensive care patients. This study is essential in establishing the feasibility of inspiratory muscle training in Study 5.

Study 2 focuses on the clinimetric properties of the Acute Care Index of Function (ACIF) as a tool to quantify physical activity levels in intensive care patients, and is a requirement for the design of Studies 3, 4 and 5.

Study 3 is an observational study that describes the inspiratory muscle strength, endurance and dyspnoea scores of a cohort of patients who have successfully weaned from invasive mechanical ventilation. This study compares the cohort to be studied in Studies 4 and 5 with those described in previous literature. This is important as physiotherapy and ventilation practices have evolved considerably over the past 10 years (e.g. focus on early mobilisation, minimisation of sedation and move towards spontaneous modes of ventilation).

Study 4 is a randomised trial of inspiratory muscle training in patients who have successfully weaned from mechanical ventilation of at least 7 days' duration, but whom were not eligible for inspiratory muscle training whilst mechanically ventilated (e.g. due to delirium). This study ascertains whether inspiratory muscle training offers superior benefits over usual care in the 2 weeks following weaning from mechanical ventilation, and includes measures of dyspnoea, quality of life and physical activity as well as inspiratory muscle strength and endurance.

Study 5 is a protocol for a randomised trial of inspiratory muscle training commenced while patients are ventilator-dependent. This study is presented as a protocol only, as slow recruitment has prohibited its inclusion in the current thesis. At time of submission, a total of 48 of 70 patients have been recruited since February 2011, and the study will continue until the target number of patients is reached (anticipated completion 2017).

Finally, the results of these studies (with the exception of Study 5) will be discussed with reference to the existing literature, and recommendations for future studies will be made.

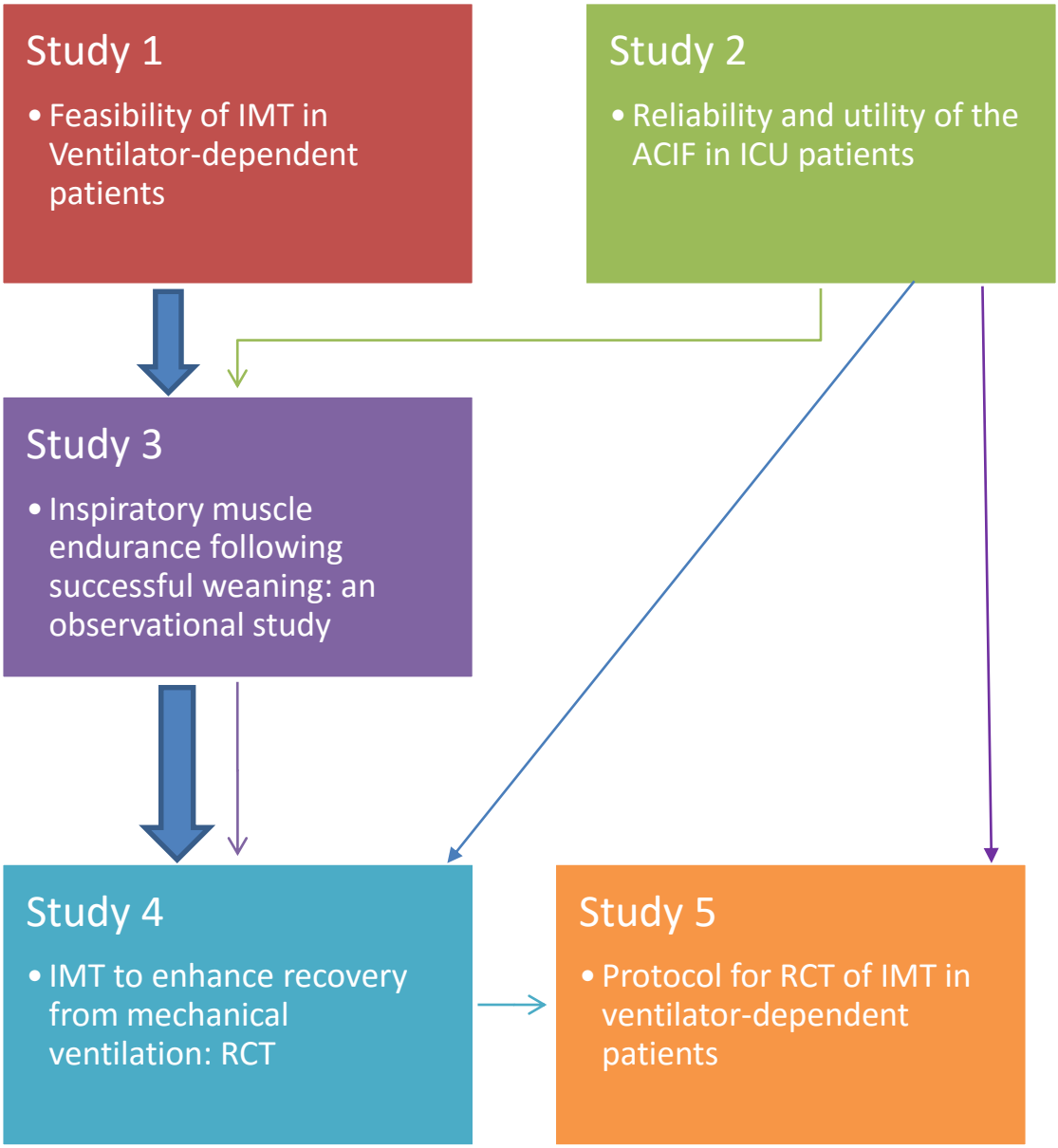


Figure 3: Flow of studies included in this thesis.

CHAPTER 2: Study 1

Inspiratory Muscle Training in Ventilator-Dependent Patients:

A Feasibility Study

This chapter has been published as an original research publication in the peer-reviewed journal Intensive and Critical Care Nursing and is reproduced with permission (Appendix C): http://www.ncbi.nlm.nih.gov/pubmed/22340987

Bissett B, Leditschke IA, Green M (2012). *Specific inspiratory muscle training is safe in selected patients who are ventilator-dependent: a case series.* Intensive & Critical Care Nursing **28** (2):98-104.

INTRODUCTION

Mechanical ventilation results in significant respiratory muscle weakness which is correlated with duration of ventilation (Hermans et al., 2010) and remains detectable 7 days following successful weaning (Chang et al., 2005a). Evidence indicates that this weakness is due in part to excessive atrophy and proteolysis in respiratory muscles compared to other skeletal muscles (Levine et al., 2008). This muscle weakness may hinder weaning from mechanical ventilation and thus contribute to the known high health care costs of prolonged mechanical ventilation (Cox et al., 2007, Unroe et al., 2010). Somewhat surprisingly, the possibility of strengthening these weakened respiratory muscles is a relatively recent area of research in intensive care medicine.

In ventilated patients, ventilator manipulations have not been found to provide an effective training stimulus for inspiratory muscles (Caruso et al., 2005). In contrast, two recent randomised trials have demonstrated favourable results with inspiratory muscle training using a removable threshold device. The first (Cader et al., 2010) studied inspiratory muscle training in 41 ventilated patients aged 70 and older, and found that a training regime of 5 minutes twice-daily, commencing at an intensity of 30% of maximum, resulted in a significant increase in inspiratory muscle strength (mean difference in MIP of 7.6 cm H_2O 95% CI 5.8 to 9.4) and a reduction in the weaning period (mean difference 1.7 days, 95% CI 0.4 to 3.0). The second study (Martin et al., 2011) investigated inspiratory muscle training in 69 patients who had failed conventional weaning methods. These researchers used a high-intensity interval training strategy (i.e. 4 sets of 6 to 10 breaths), employing the highest tolerable resistance. In the inspiratory muscle training group, inspiratory muscle strength increased from 44.4 to 54.1 cm H_2O (mean values), whereas no significant difference was detectable in the sham group. Furthermore there were significantly more patients successfully weaned in the inspiratory muscle training group at 28 days following initiation of training (treatment group 71%, 95% CI 55% to 84%; sham group 47%, 95% CI = 31% to 63%). These results are consistent with several earlier case reports that indicated that inspiratory muscle training is associated with increased inspiratory muscle strength and favourable weaning outcomes (Bissett and Leditschke, 2007, Martin et al., 2002, Sprague and Hopkins, 2003).

However, none of these studies specifically measured the physiological responses to inspiratory muscle training (i.e. effects of inspiratory muscle training on blood pressure, heart rate, respiratory rate or oxygen saturation). Given the potential benefits of inspiratory

muscle training, detailed information about the safety and physiological effects of inspiratory muscle training in this population would be relevant to clinicians when determining whether inspiratory muscle training is suitable for a specific ventilator-dependent patient. It would also be useful to establish whether supplemental oxygen is required to prevent desaturation with inspiratory muscle training in ventilated patients, as some studies have included supplemental oxygen (Martin et al., 2002, Sprague and Hopkins, 2003) but others have not (Bissett and Leditschke, 2007, Martin et al., 2011).

Furthermore, there is very limited evidence regarding the incidence of adverse events in response to inspiratory muscle training (i.e. new arrhythmia, blood pressure or heart rate changes > 20% or requiring remedial intervention, oxygen desaturation >10% or requiring remedial intervention, detachment of equipment or lines, pneumothorax immediately following intervention) (Zeppos et al., 2007). While other physiotherapy interventions in intensive care have been found to be safe with an incidence of <0.2% of adverse physiological outcomes (Zeppos et al., 2007), it is not known how this relatively novel treatment compares with standard physiotherapy in terms of safety.

Thus the present study aimed to answer the following research questions:

1. Is specific inspiratory muscle training with a threshold device, but without supplemental oxygen, safe in selected ventilated patients in terms of both physiological responses and adverse events?
2. Does inspiratory muscle strength increase from baseline to weaning from the ventilator with a high intensity interval-based inspiratory muscle training protocol in a heterogeneous group of ventilator-dependent patients?

METHOD

Design

A study of prospectively collected data for a cohort of 10 tracheostomised adults in the intensive care unit who had failed to wean from mechanical ventilation and subsequently underwent inspiratory muscle training was conducted. Inspiratory muscle training was instituted when patients met the suitability criteria described below and was continued daily (if clinically appropriate) until successful weaning or death. The study was approved by the Australian Capital Territory Health Human Research Ethics Committee and patients provided their own informed consent (Appendix B).

Participants

Patients were selected for inspiratory muscle training if they had failed weaning from mechanical ventilation via usual methods (i.e. progressively increasing time spent breathing through a humidified t-piece) and met the inclusion criteria for our inspiratory muscle training protocol (Bissett and Leditschke, 2007), which requires patients to be alert and able to cooperate with training, able to rate their dyspnoea via a modified Borg scale (Borg, 1982) by either mouthing words or pointing, requiring stable and not excessive ventilatory support (i.e. PEEP < 10 cm H_2O, FiO_2< 0.60), having a tracheostomy in situ and being otherwise medically stable.

Intervention

A program of daily inspiratory muscle training with a threshold inspiratory muscle trainer was initiated. This commercially available device allows the setting of specific training intensities between 9 and 41 cm H_2O and has been found to be reliable in guaranteeing pressure levels independent of patient flow rates (Gosselink et al., 1996).

The training method used was very similar to that described previously (Bissett and Leditschke, 2007, Martin et al., 2002, Martin et al., 2011, Sprague and Hopkins, 2003). Patients were positioned in the high Fowler's (high sitting) position and were briefly removed from the ventilator, with the inspiratory muscle training device attached directly to the tracheostomy via a simple connector (Figure 4). Unlike some previous studies (Cader et al., 2010, Martin et al., 2002, Sprague and Hopkins, 2003), no supplemental oxygen was applied.

Each session the physiotherapist supervised the completion of 3 to 6 sets of 6 breaths at a training threshold that generated a rate of perceived exertion (RPE) of between 6 and 8 out of 10 using a modified Borg scale (Borg, 1982). Inspiratory efforts that did not trigger the threshold valve to open, detected by an audible sound, were not counted in the set and the patient was instructed to repeat the effort until a successful breath was achieved.

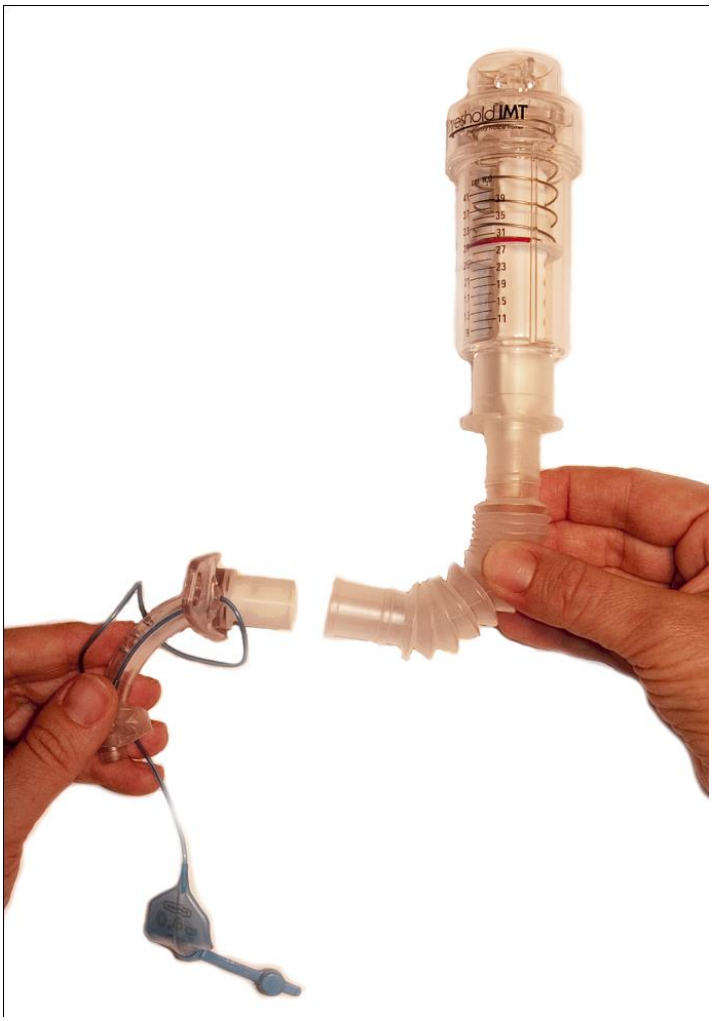


Figure 4: Attachment of the training device to a tracheostomy tube via a connector

Rests were allowed between sets as the patient desired, meaning the patient was returned to the ventilator with typical rest times of 1 to 2 minutes between sets. Each time the patient's RPE during resisted breaths was lower than 6, the training pressure was increased by 2 to 4 cm H_2O. Training continued until patients were weaned from the ventilator.

Outcome measures

Primary outcome: The primary outcome was the physiological response to inspiratory muscle training, as reflected by the following measures: heart rate, mean arterial pressure (MAP), oxygen saturation and respiratory rate. Heart rate, respiratory rate and oxygen saturation were monitored non-invasively using standard intensive care electrocardiograph and pulse oximetry equipment, while MAP was monitored continuously via the arterial line where in situ, or non-invasively where the arterial line had been removed. All measures were monitored continuously and transcribed from the monitors by the treating therapist immediately on completion of each set of inspiratory muscle training (where each set was < 10 seconds' duration).

Secondary outcomes: The number of adverse events (i.e. new arrhythmia, blood pressure or heart rate changes > 20% or requiring remedial intervention, oxygen desaturation >10% or requiring remedial intervention, detachment of equipment or lines, pneumothorax immediately following intervention) (Zeppos et al., 2007) in response to inspiratory muscle training was recorded. Inspiratory muscle training training pressures (cm H_2O) for a given RPE (6 to 8 out of 10, modified Borg scale) were recorded each session as a surrogate of inspiratory muscle strength.

Data analysis

Paired t-tests were used to compare initial (i.e. following set 1) and final (following set 3, 4 or 5, depending on each patient's training level) values of each physiological variable within the second treatment session. The second session was selected to avoid the learning effects and suboptimal intensities likely during the first session, while still reflecting the acute response to inspiratory muscle training. A paired t-test was also used to compare training pressures on initiation of treatment and on completion. Statistical significance was considered as $p<0.05$. The mean difference (MD) and 95% confidence intervals are reported for each variable.

RESULTS

Flow of participants through the study

The characteristics of patients who underwent inspiratory muscle training are presented in Table 3.

Adherence to study protocol

A total of 195 inspiratory muscle training treatment sessions were delivered to the 10 patients studied. In addition to these sessions, there were more than 50 occasions where inspiratory muscle training was scheduled but patients failed to meet the inspiratory muscle training suitability criteria on that day (e.g. became cardiovascularly unstable, required increased sedation for procedures or investigations). In these instances, inspiratory muscle training was suspended until patients met the suitability criteria. Only 1 patient had no interruptions to their daily inspiratory muscle training.

Table 3: Characteristics of patients, training parameters and weaning outcomes in Study 1

	Sex	Age (yr)	Primary Diagnosis	Day commenced IMT	ICU LOS	Training sessions completed	Highest training pressure	Weaning outcome
Patient 1	Female	64	GBS	12	24	10	41	Weaned
Patient 2	Male	79	Emergency bowel resection	17	29	11	38	Weaned
Patient 3	Male	64	CIDP	30	194	28	31	Weaned
Patient 4	Female	55	Septicemia	13	28	10	34	Weaned
Patient 5	Female	74	Interstitial pneumonitis	14	28	6	15	Died
Patient 6	Female	81	Sepsis, oesophageal tear	13	37	3	41	Weaned
Patient 7	Male	75	GBS	96	237	60	33	Weaned
Patient 8	Female	51	GBS	17	49	13	38	Weaned
Patient 9	Male	46	GBS	17	219	34	41	Weaned
Patient 10	Female	24	Polymyositis (GVHD)	13	212	20	11	Died

IMT = inspiratory muscle training; ICU LOS = Intensive Care Unit Length of Stay; GBS = Guillain-Barre Syndrome; CIDP = Chronic inflammatory demyelinating neuropathy; GVHD = Graft vs Host Disease (on background of leukaemia)

Safety of inspiratory muscle training

No adverse events were recorded in response to inspiratory muscle training across the 195 treatments. Figure 5 demonstrates the physiologic effects of inspiratory muscle training for patients undergoing their second inspiratory muscle training session, while still physiologically vulnerable from critical illness, but having overcome the learning requirements of training in session 1. No significant changes in heart rate (MD 1.3 bpm, 95% CI -2.7 to 5.3), MAP (MD -0.9 mmHg, 95% CI -6.4 to 4.6), respiratory rate (MD 1.2 bpm, 95% CI -1.1 to 3.5 bpm) or oxygen saturation (MD 1.2%, 95% CI -0.6 to 3.0) were detected in response to treatment (Figure 5). Although one patient experienced a drop in oxygen saturation below 90% (from 92%), this was transient, had normalised less than 60 seconds after return to ventilation and did not require any other intervention, thus was not considered to be an adverse event.

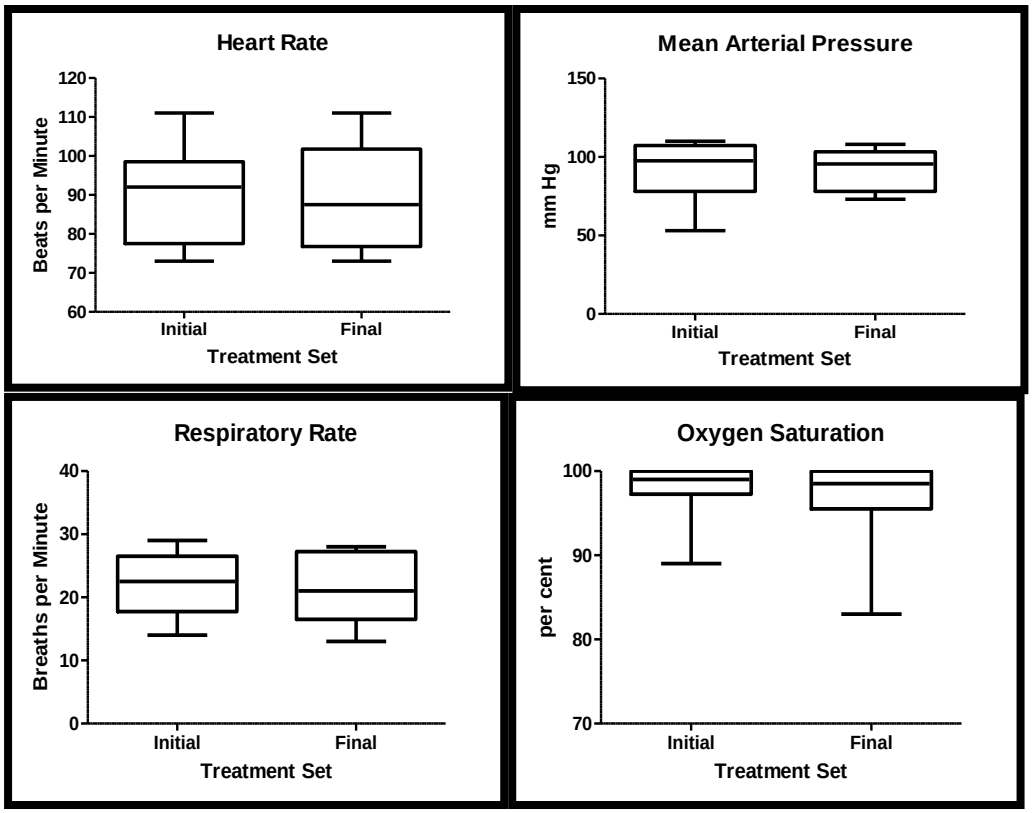


Figure 5: Physiological parameters following initial and final sets within 1 IMT training session (where box indicates median and interquartile range and whiskers indicate maximum and minimum values).

Research question 2

While individual training patterns varied there was a significant overall increase in training pressures (MD 18.6 cm H_2O, 95% CI 11.8 to 25.6) (Figure 6). The two patients who did not increase their final pressures above 20 cm H_2O died due to factors unrelated to inspiratory muscle training or ventilatory failure (i.e., pancreatitis, complicated severe sepsis). The remaining eight patients successfully weaned from ventilation and were able to be discharged to the ward. None required subsequent readmission to the intensive care unit.

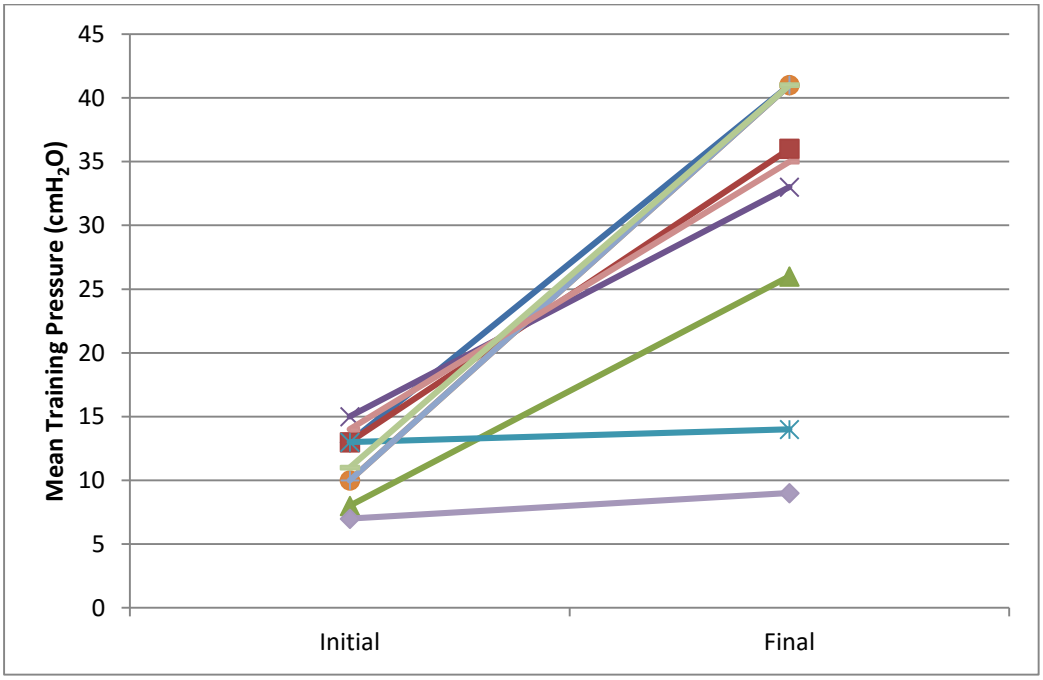


Figure 6: Changes in mean training pressures over entire training period for each participant

DISCUSSION

This study demonstrates that a strength-based inspiratory muscle training protocol using a threshold device, without supplemental oxygen, is safe for use in selected ventilated patients with no deleterious effects on physiological parameters or clinically significant adverse events recorded. The high mortality rate (20%) found in this study is not alarming given the known mortality of intensive care patients who are ventilated longer than 7 days (13% in our unit, internal audit data Canberra Hospital 2009). The wide variation in intensive care unit length of stay is not surprising given the heterogeneous patient group.

Our findings contrast with those of Caruso et al (2005) who did not use a threshold device but instead used ventilator manipulations to perform inspiratory muscle training. The Caruso study failed to detect an increase in maximal inspiratory pressure in the inspiratory muscle training group and of 167 treatments, also reported 23 cases (14%) of adverse physiological outcomes (i.e. desaturation, tachypnoea, haemodynamic instability and arrhythmia). However, Caruso et al used a training intensity of 10 – 40% which may have been inadequate for training effects, and included patients from day 2 of ventilation who may not have been sufficiently alert to actively participate in training. Furthermore, their training method did not require removal from ventilatory support, and thus their findings may not be relevant to the threshold inspiratory muscle training method employed in our study.

Inspiratory muscle training with a threshold device necessitates disconnection from ventilatory support for brief supervised periods and requires patients to fully and actively participate in training. There may be important psychological advantages of short, intense and safely monitored training sessions where patients can build confidence breathing independently. Previously threshold-based inspiratory muscle training has been found to have significant psychological benefits in other populations including patients with cystic fibrosis (Enright et al., 2004) and healthy people (Chatham et al., 1999).

The improvements in inspiratory muscle training pressures demonstrated in this case series are consistent with the inspiratory strength improvements reported in a recent randomised trial of inspiratory muscle training in older ventilated patients (Cader et al., 2010). However our patient sample was more heterogeneous, including younger patients and those with known neuromuscular disease. Furthermore, our training regime is a strength-based (high resistance, low repetition) protocol as opposed to the endurance

protocol (lower resistance, longer duration) used in the study by Cader et al (2010). Whereas some ventilated patients may not tolerate the duration of training required in the Cader protocol (i.e. 5 minutes breathing through resistance), they may be able to tolerate the shorter, more intense training of an interval program (6 high-resistance breaths per set with rests between sets).

While the improvements in training pressures observed in this case series cannot be attributed to inspiratory muscle training alone (due to the absence of a control group) the magnitude of change is consistent with the increased inspiratory muscle strength reported by Martin et al(Martin et al., 2011), confirming that the training strategy used in the present study is comparable in terms of intensity. We can therefore be confident that our findings regarding physiological response and safety are not due to a more conservative training protocol, but rather could be applied more generally to high intensity interval-based inspiratory muscle training in ventilator-dependent patients. Thus, it seems reasonable to conclude that supplemental oxygen is not essential for inspiratory muscle training with high intensity interval-based inspiratory muscle training in ventilator-dependent patients as it does not result in significant tachypnoea nor oxygen desaturation.

The decision to apply strength training to what is essentially an endurance muscle (the diaphragm) may seem curious. However it has been consistently demonstrated in athletic populations that strength training of the diaphragm (i.e. high resistance, low duration inspiratory muscle training) also enhances endurance (Gething et al., 2004b, Johnson et al., 2007, Enright et al., 2006, Bailey et al., 2010). Possible mechanisms include increased proliferation of both Type 1 and Type 2 muscle fibres (Ramirez-Sarmiento et al., 2002) and reduced lactate production (Brown et al., 2008), which may in turn enhance the muscle's endurance properties. The argument that spontaneous breathing trials alone provide sufficient endurance training (i.e. low resistance over a longer period of time) is not supported by the residual impaired fatigue resistance found in patients following successful weaning (Chang et al 2005), in addition to the substantial proportion of patients who fail to wean with this strategy and thus experience prolonged weaning and all the associated costs and challenges (Unroe et al 2010).

A limitation of this study is that it did not capture the patient's subjective experience of undergoing inspiratory muscle training. The psychological aspects of ventilator-dependence should not be under-estimated, with a recent study reporting that up to 88%

of patients find the experience of intubation and ventilation moderately to severely stressful (Samuelson, 2011). Whether inspiratory muscle training could reduce this stress remains to be determined. Anecdotally, our patients not only tolerated inspiratory muscle training, but appeared to find the specific feedback of the level of training pressure to be somewhat motivating. Future studies should consider capturing the patient's perspective in analysing the utility of inspiratory muscle training in this group.

Further randomised trials are indicated to determine which type of inspiratory muscle training protocol is optimal and whether inspiratory muscle training attenuates ventilator-associated respiratory muscle weakness or reduces the duration of ventilation for intensive care patients across the spectra of age and acuity. In the interim, threshold-based inspiratory muscle training can be considered a safe and feasible treatment option in selected ventilated patients and may be a useful adjunct to ventilatory weaning. In the context of a multidisciplinary approach to critical care rehabilitation, inspiratory muscle training may be an important element of a comprehensive treatment strategy. Future studies should also consider whether the known strength gains of inspiratory muscle training translate into meaningful patient-centred outcomes such as functional ability and quality of life.

CHAPTER 3: Study 2

The Acute Care Index of Function in Intensive Care Patients:

A reliability and utility study

This chapter has been published as an original research publication in the peer-reviewed journal Heart and Lung and is reproduced with permission (Appendix C):

http://www.ncbi.nlm.nih.gov/pubmed/26542832

Bissett B, Green M, Marzano V, Byrne S, Leditschke IA, Neeman T, Boots R, Paratz J (2016). *Reliability and utility of the acute care index of function in intensive care patients: an observational study.* Heart and Lung (in press).

INTRODUCTION

Over the past decade, clinicians working in intensive care units have started to recognise the adverse effects of immobility. Lack of early mobilisation in intensive care patients is associated with longer duration of hospital stay (Morris et al., 2008), and increased risk of readmission and mortality (Morris et al., 2011). In contrast, early mobilisation of intensive care patients results in shorter duration of ventilation, better functional outcomes and reduced delirium (Schweickert et al., 2009). Not surprisingly, there has been a worldwide paradigm shift towards early mobilisation and rehabilitation of intensive care patients (Harrold et al., 2015, Schweickert et al., 2009), including those who in the past may have been managed with deep sedation and immobility.

The shift towards early rehabilitation in intensive care has been enabled through a willingness of multidisciplinary teams to overcome the barriers to early mobilisation (Leditschke et al., 2012, Harrold et al., 2015, Honiden and Connors, 2015), including minimisation of sedation which is thought to contribute to delirium and poor outcomes (Hall et al., 2009). Through effective collaboration of nursing, medical and physiotherapy staff, intensive care patients are now achieving higher levels of physical function in the acute phase of their illness, including mobilisation whilst still ventilator-dependent (Harrold et al., 2015). However, while we explore the limits of physical function in ICU patients, the lack of accurate and reliable tools to quantify physical function in this group presents a new challenge.

There has been recent interest in establishing the clinimetric properties of tools which can robustly describe physical function in a heterogeneous ICU population (Parry et al., 2015a). In the last 3 years, tools have been designed to specifically measure physical function in intensive care patients such as the Physical Function in ICU Tool (P-FIT) (Denehy et al., 2013), the Chelsea Critical Care Physical Assessment tool (CPax)(Corner et al., 2014) and the ICU Mobility Scale (IMS)(Hodgson et al., 2014). All these tools have demonstrated inter-rater reliability. However to our knowledge, none of these tools have been used to measure physical function for intensive care survivors beyond their intensive care admission. While early physical rehabilitation in intensive care is of great importance, much of the rehabilitation continues beyond intensive care discharge. A tool that could be used to describe physical function across the continuum of intensive care and rehabilitation would be advantageous in terms of allocating rehabilitation resources, as

well as determining which interventions improve physical function in the short and long term for intensive care survivors.

The Acute Care Index of Function (ACIF) tool was developed in 1988 to measure the physical function of patients with acute neurological problems (Roach and Van Dillen, 1988) (Figure 7). It has excellent inter-rater reliability (intraclass correlation coefficient 0.98) and validity in patients with neurological disease (Van Dillen and Roach, 1988). More recently it has been suggested that the ACIF is currently utilised by clinicians to measure physical function in other patient populations, including those with cardiopulmonary disease, however this evidence is purely anecdotal (Scherer and Hammerich, 2008). Although the tool was developed 27 years ago, and length of stay may have changed over this time for acute care patients, its construct validity remains relevant, covering four main domains of function including mental status, bed mobility, transfers and mobility. The utility of the ACIF in broader patient populations is appealing due to its ready availability, low cost and minimal training required.

For the past five years, we have been utilising the ACIF to map the physical function trajectories of intensive care patients from intensive care unit admission through to hospital discharge (Bissett et al., 2012d, Latham et al., 2013). Due to the lack of established clinimetric properties of the ACIF in an intensive care population, the objectives of this study were to establish the inter-rater reliability of the ACIF in a heterogeneous sample of intensive care patients, and in the absence of a gold-standard by which to test validity, to describe the relationship between the ACIF and the IMS. As a crude approximation of construct validity, we also sought to ascertain whether ACIF scores at intensive care discharge could predict the recovery trajectory beyond the intensive care stay.

Thus the aims of Study 2 were to answer the following questions:

1) Does the ACIF have acceptable inter-rater reliability in a heterogeneous sample of intensive care patients?
2) What is the relationship between the ACIF and the IMS?
3) Can the ACIF measured at intensive care discharge predict hospital discharge destination?

METHOD

Ethics, consent and permissions

This study was approved by the Australian Capital Territory Health Human Research Ethics Committee (ETH.14.213), including a waiver of patient consent as the study did not require change to usual practice for the patient. All 8 staff provided verbal consent to participate in this study.

Design and setting

In this prospective observational study, data was collected from September to December 2014 inclusive in a 31-bed tertiary ICU (Canberra, Australia) with a mixed surgical / medical population, including trauma patients. This ICU has a standard practice of minimal sedation and early mobilisation, as described elsewhere (Leditschke et al., 2012).

Participants

A convenience sample of 8 physiotherapists participated in the study including the senior intensive care physiotherapist, two senior physiotherapists each with more than 10 years' experience, as well as the rotating junior staff working in the intensive care unit throughout the duration of the study. No staff were excluded from the study.

The patients were selected as a convenience sample of all intensive care patients from Day 3 of admission onwards, such that whenever 2 physiotherapists were simultaneously involved in the assessment of a patient in intensive care during the study period, the patient was enrolled in the study. Day 3 of intensive care stay was selected to exclude patients who were admitted to the intensive care unit with minor illness or for observation only (e.g. following elective surgery without complication) as these patients rarely require substantial assistance to regain independent function. Apart from those whose intensive care unit stay was shorter than 2 days, no patients were excluded from the study.

Measures

The outcome measures used included the ACIF tool as previously published (Roach and Van Dillen, 1988) (Figure 7) where a score of 1.00 indicates no loss of function, and a score of 0.00 indicates worst possible function. Sub-components of the ACIF include 'Mental Status', 'Bed Mobility', 'Transfers' and 'Mobility'. No adaptations were made from the original tool.

Acute Care Index of Function

The ACIF consists of 20 items that are divided into 4 subsets:

Subscale/Item	Grading			Score
	No		Yes	
Mental status (MS)				MS Score = (/6)
1. *Verbal commands*	0		2	
2. *Commands*	0		1	
3. *Learning*	0		2	
4. *Safety awareness*	0		1	
	Unable	Dependent	Independent	
Bed Mobility (BM)				BM Score = (/40)
6. *Roll supine to right*	0	4	10	
7. *Roll supine to left*	0	4	10	
8. *Supine to sit*	0	4	10	
9. *Sit to supine*	0	4	10	
Transfers (T)				T Score = (/60)
10. *Chair to bed*	0	5	10	
11. *Bed to chair*	0	5	10	
12. *Sit to stand*	0	5	10	
13. *Stand to sit*	0	5	10	
14. *Sitting balance*	0	5	10	
15. *Standing balance*	0	5	10	
Mobility (M)				M Score = (/70)
16. *Gait with device (15m)*	0	14	20	
17. *Gait without device (15m)*	0	21	30	
18. *Ascend 5 stairs*	0	7	10	
19. *Descend 5 stairs*	0	7	10	
20. *Propel wheel chair*[a]	*0*	*14*	*20*	
21. *Set-up wheel chair*[a]	*0*	*7*	*10*	
Total Score: (1) x MS + (1) x BM + (2) x T + (2) x M = …/6 =				

Unable: Patient cannot physically perform the activity

Dependent: Independent: Patient assists to perform the activity but requires physical or verbal assistance.

Patient performs the activity without verbal or physical assistance.

[a]Wheelchair item disregarded unless relevant to patient. For relevant patients M Score = (/100)

Figure 7: Acute Care Index of Function tool for quantifying physical function (Reproduced with permission).

All health professionals involved in the study attended a 30 minute briefing about the use of the tool and the processes involved in the study. Whenever 2 assessors were present throughout a patient assessment in intensive care, each assessor independently completed an ACIF form (one electronic, one paper-based). The paper-based forms were stored in a locked filing cabinet and were not accessible to any other staff until study completion.

The assessor completing the electronic ACIF form also completed an IMS score, an 11-point ordinal scale of function (Hodgson et al., 2014), where a score of 0 indicates function is 'nothing' and 10 indicates 'walking independently without a gait aid'. ACIF and IMS scores were routinely collected electronically for all intensive care patients at least once per week beyond Day 3 of admission, and on intensive care unit discharge.

Data including duration of ventilation, duration of intensive care stay, duration of hospital stay and hospital discharge destination for each patient were obtained from hospital databases by research nurses not directly involved in the project. We grouped discharge destination as 'home' or 'not home', as in our experience patients who discharge directly home from our facility require substantially less rehabilitation than those who either require further rehabilitation in another facility prior to discharge home, or those whose final discharge destination is a residential care facility.

Data analysis

Extrapolating from previous studies of inter-rater reliability in functional measures (Hodgson et al., 2014, Van Dillen and Roach, 1988) a sample size of 100 ACIF assessments was chosen, allowing a power of 80% ($p = 0.05$) to detect a difference of 0.10 on the ACIF scale. To determine inter-rater reliability, we calculated Intra-class Correlation Coefficients (ICC (1,1)) for total ACIF scores as well as subcomponent ACIF scores, using variance components analysis to account for variance both between assessors and within individual patients. We used parametric correlation to describe the relationship between ACIF scores and IMS scores, with significance at the $p< 0.05$ level. To explore the sensitivity and specificity of ACIF scores at intensive care discharge to predict hospital discharge destination, we created a dichotomous variable (discharge home versus not home) and generated a receiver operating characteristic (ROC) curve. Based on our previous research (Latham et al., 2013), we chose an ACIF level of 0.40 level a priori to test sensitivity and specificity. Statistical analyses were performed using SPSS version 22.

RESULTS

Participants

Eight assessors, all physiotherapists, participated in the study (male = 1), with a mean clinical experience of 8.4 years (range 1.5 – 19 years). Assessors reported that, following their usual assessment procedures, completion of the ACIF tool took approximately 1 to 2 minutes.

A total of 100 patient assessments were included in the study, from 42 unique patients (11 female).

Table 4

Table 3 describes the demographic data of these 42 patients, including their hospital length of stay and hospital discharge destination.

Table 4: Characteristics of patients included in Study 2

Patient Characteristics	N= 42
Age (yr), mean (SD, range)	59 (19, 16-88)
Sex, n female (%)	11 (26)
APACHE II on ICU admission (0-30), mean (SD)	19 (7)
Duration of ICU Stay (days) (mean ± SD) (range)	19 ± 29 days (2 – 119)
Hospital Length of Stay (mean ± SD) (range)	51 ± 37 days (6 – 141)
Duration of mechanical ventilation (mean ± SD) (range)	12 ± 25 days (0 – 118)
Discharged home from hospital (%)	15 (35%)
Discharged to rehabilitation / other hospital (%)	18 (43%)
Did not survive hospital admission (%)	9 (21%)

SD = Standard Deviation; APACHE II = Acute Physiology and Chronic Health Evaluation Score

Inter-rater reliability

The total ACIF scores measured throughout the study period ranged from 0.00 to 0.90 out of 1.00, with a mean score of 0.30 (standard deviation 0.23). On 10 occasions, total ACIF was rated as 0 (floor effect of 0/1.00= 10%) while no patients scored 1.00 (ceiling effect of 1.00/1.00 = 0%). The correlation between total ACIF scores between independent assessors across the 100 patient assessments is represented in Figure 8.

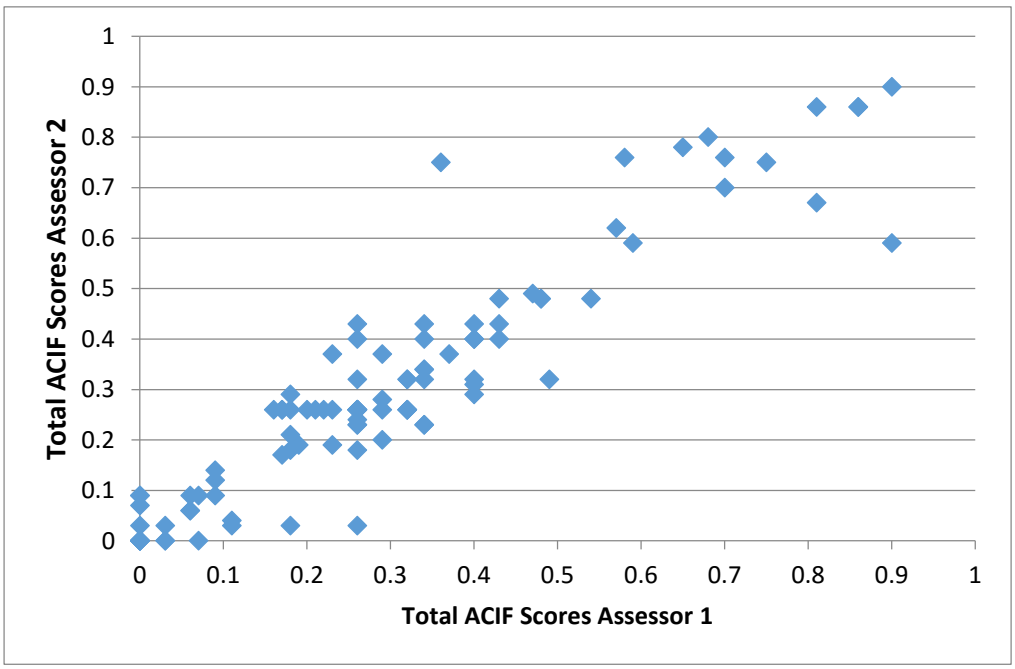


Figure 8: Correlation between total ACIF scores for 2 independent assessors in intensive care patients

Intra-class Correlation Coefficients (1,1) for ACIF scores (including sub-components) are presented in Table **5**, with an ICC of 0.94 for total ACIF scores, indicating extremely strong agreement between assessors.

Table 5: Inter-rater reliability of the Acute Care Index of Function in intensive care patients

ACIF COMPONENT	**ICC VALUE**
Mental Status	0.83
Bed Mobility	0.81
Transfers	0.93
Mobility	0.94
Total ACIF score	0.94

Relationship between ACIF and IMS

IMS scores ranged from 0 to 10 across the 100 assessments. Total ACIF scores were strongly correlated with IMS scores (r = 0.84, p = 0.01). However there was notable spread of ACIF scores within each IMS category as represented in Figure 9.

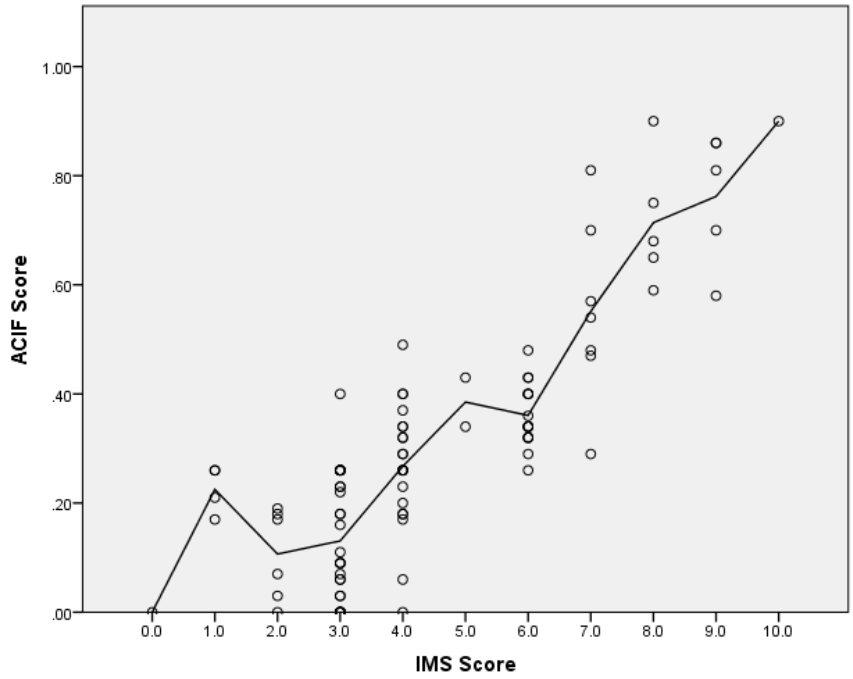


Figure 9: Correlation between total ACIF scores and IMS scores in intensive care patients

Utility of ACIF in predicting discharge destination

Of the 42 individual patients included in this study, 15 were discharged directly home from hospital, 9 died in hospital, and the remainder were discharged to other hospitals for further rehabilitation prior to discharge home. ACIF scores at intensive care discharge had good discrimination for predicting discharge home (area under ROC = 0.79, 95% CI 0.64 – 0.89) (Figure 10). An ACIF score of < 0.40 on intensive care discharge predicted hospital discharge to a destination other than home (i.e. another hospital, residential care home or death) with a sensitivity of 0.78 (specificity of 0.47).

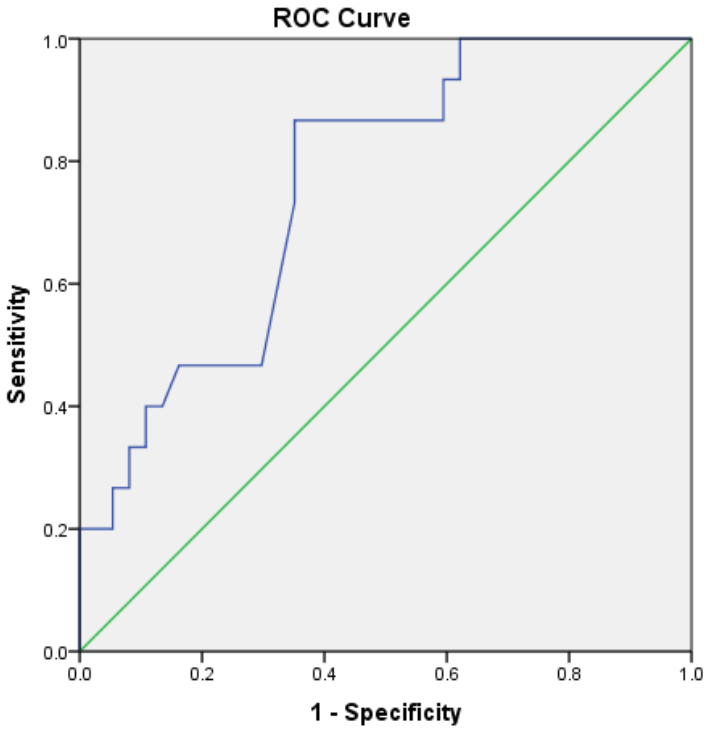


Figure 10: Receiver operating characteristic curve for ACIF score on intensive care discharge predicting discharge directly home from hospital

DISCUSSION

The major finding of this study, that the ACIF has very strong inter-rater reliability (ICC 0.94), is consistent with previous clinimetric investigation of the ACIF (Van Dillen and Roach, 1988). Although the inter-rater reliability of the ACIF in this study is not as high as that found by Van Dillen and Roach (1988) in patients with neurological impairment (ICC 0.98 – 1.00), the previous study was in a less naturalistic setting (using video footage) where one would anticipate higher concordance. In contrast, our study required in vivo application of the tool in an authentic clinical environment, and our results confirm that the excellent inter-rater reliability of the ACIF is not limited to neurological patients but also extends to intensive care patients.

Both the ACIF (ICC 0.94) and IMS (ICC 0.8) (Hodgson et al., 2014) have acceptable inter-rater reliability to be useful in an intensive care context. Whilst this study demonstrated that the ACIF and IMS correlate strongly across the spectrum of physical function in intensive care patients, there was significant spread of ACIF scores within each IMS category. This spread could be attributed to the fact that ACIF captures more subtle dimensions of function within each category, due to the broader ranges of activities covered and the distinction between levels of assistance required for various tasks. These differentiated degrees of function may be useful in measuring change over time, particularly for patients who make slow progress. Furthermore, the ACIF includes mental status as an element of overall function, which IMS does not. Mental functioning may be important in ascertaining patients' levels of independence with physical function as they recover from their intensive care admission (e.g. safety awareness or capacity for learning new tasks).

A limitation of this study is that it did not make direct comparisons with the P-FIT. The recently modified P-FIT incorporates gait cadence, knee extension and shoulder flexion measures, as well as assessment of the level of assistance required for sit-to-stand. However, these can only be assessed if patients meet the criteria for wakefulness, otherwise they are assigned a score of zero (Denehy et al., 2013). Previous studies have quantitatively described the significant floor effect (32%) of the P-FIT which may limit its usefulness in the intensive care unit, particularly early in the intensive care admission (Nordon-Craft et al., 2014). In contrast, we found that the ACIF had only a small floor effect (10%) and no ceiling effect in intensive care patients from Day 3 of admission onwards. Moreover, the ACIF does not require specific measures (e.g. muscle testing) to be

conducted in addition to a standard physiotherapy functional assessment, and is typically completed in one to two minutes. Accordingly, we do not use the P-FIT in our intensive care unit and have instead found the ACIF to be a time-efficient routine functional measure which differentiates functional performance across the spectrum.

Like both the P-FIT and the CPax, we found that the ACIF has predictive utility for hospital discharge destination from intensive care discharge. Patients at intensive care discharge whose ACIF scores are below 0.40 could be identified as high risk for not returning directly home, and this may be important for allocation of rehabilitation resources. In the absence of a gold standard with which to compare, this predictive utility also provides some crude evidence of construct validity of the ACIF in intensive care patients.

Future studies may compare the relative merits of the ACIF and the CPax for measuring physical function in intensive care patients. Like the ACIF, the CPax is completed by physiotherapists within 1 to 2 minutes following a standard assessment, and has robust inter-rater reliability and construct validity (Corner et al., 2014). In contrast to the P-FIT, the CPax does not have substantial floor (3.2%) or ceiling (0.8%) effects. However, the CPax differs from the ACIF in that it also captures respiratory function and cough, but does not include mental status. The relative value of these subcomponents should be explored, as they may have an impact on the usefulness of each measure. Furthermore, to our knowledge the CPax has not been used to describe recovery trajectories beyond intensive care stay. While the authors of the CPax suggest that there will never be a single tool to capture physical function across hospital admission (Corner et al., 2014), our preliminary work suggests that the ACIF tool may achieve this (Latham et al., 2013) and deserves further investigation.

Recently the Functional Independence Measure (FIM) has also been used to describe the trajectory of recovery for intensive care survivors (Herridge et al., 2015). The FIM is well-established as a reliable and valid measure of physical function in the rehabilitation setting (Hamilton et al., 1994). However in Australia, the FIM requires both purchase of a licence and specific training, including credentialing of staff every two years. As the ACIF is freely available and does not require specific training, the ACIF has been a more feasible alternative to adopt in our institution.

We agree that clinicians and researchers around the world should establish a core set of physical function outcome measures for intensive care patients (Parry et al., 2015b). Both clinicians and researchers need measurement tools that are readily available, efficient and easy to use, inexpensive and clinimetrically sound. Ideally, a single tool could be used to measure a patient's physical function from intensive care unit admission right through to hospital discharge. This study provides some evidence that the ACIF should be considered in this discussion, in view of its excellent reliability and apparent construct validity in intensive care patients, as well as its efficiency and affordability. Future studies should compare the relative merits of the available tools for measuring physical function in intensive care survivors, not just in intensive care but across the whole pathway of recovery.

The results of this study have clinical relevance for health professionals working in acute care settings. Firstly, in our experience, early mobilisation is only feasible in intensive care when nurses and physiotherapists collaborate effectively at the bedside and prioritise this time-consuming intervention. We now have a tool which can accurately and reliably measure the fruit of that collaboration. Secondly, ACIF scores will allow intensive care clinicians to objectively describe improvements in the physical function trajectory of a long-term intensive care patient, which can feel frustratingly slow at times. This information can also be shared with the patient to improve their sense of progress and self-efficacy. Thirdly and perhaps most importantly, ACIF scores at intensive care discharge can be used to inform discussion between intensive care staff and subsequent carers. In our facility, it is the experienced acute care nurses who are most likely to coordinate discharge plans and referrals for further rehabilitation for intensive care survivors. Thus ACIF scores are relevant to all acute care clinicians as they strive to maximise the physical function of patients even beyond intensive care discharge.

CONCLUSION:

The ACIF has excellent inter-rater reliability in intensive care patients. Whilst strongly correlated with the IMS, the ACIF also strongly predicts the likelihood of discharge home compared to another facility. The ACIF should be considered in the establishment of a core set of functional outcome measures for intensive care survivors.

CHAPTER 4: Study 3

Inspiratory Muscle Endurance is Impaired Following Successful Ventilatory Weaning: An Observational Study

This chapter has been published as an original research publication in the peer-reviewed journal Heart and Lung and is reproduced with permission (Appendix C):

http://www.ncbi.nlm.nih.gov/pubmed/25455911

Bissett B, Leditschke IA, Neeman T, Boots R, Paratz J (2015). *Weaned but weary: one third of adult intensive care patients mechanically ventilated for 7 days or more have impaired inspiratory muscle endurance after successful weaning.* Heart and Lung 44 (1):15-20.

INTRODUCTION

Intensive care unit patients frequently experience peripheral muscle wasting and these changes are detectable very early in the admission. Early rapid proteolysis occurs in the diaphragm muscles of ventilated patients (Levine et al., 2008). Inspiratory muscle weakness, manifesting as a reduction in maximum inspiratory pressure (MIP), is also associated with limb muscle weakness in intensive care patients (De Jonghe et al., 2007). Thus proteolysis of both the skeletal muscles and diaphragm are likely to complicate illness and affect the recovery trajectory for many intensive care patients.

The resulting diaphragmatic weakness is a potential contributor to difficulty in weaning from mechanical ventilation (Bissett et al., 2012a). However, few studies to date have measured functional endurance of the diaphragm in this patient group. This is surprising, as diaphragmatic endurance, rather than force, is required to achieve breathing independently of the mechanical ventilator.

In 2005 Chang and colleagues (Chang et al., 2005a) demonstrated that respiratory muscle endurance is impaired for some time after successful weaning from mechanical ventilation. In addition, impaired endurance is negatively associated with duration of mechanical ventilation ($r = -0.65$, $p = 0.007$).

To our knowledge, the relationship between respiratory muscle weakness (impaired strength or endurance) and global functional measures in intensive care patients (e.g. Barthel Index, Acute Care Index of Function) has not been explored. Functional status (i.e. the ability to transfer and mobilise independently) is important for longer term outcomes and quality of life. It is plausible that difficulty breathing, secondary to residual respiratory muscle weakness, may impact on the functional status of intensive care survivors. It is therefore important to establish the relationship between respiratory muscle weakness and physical function in intensive care patients.

Perceived exertion may also impact on functional status, but remains uninvestigated. In the context of mobilising intensive care patients, patient dyspnoea or perceived exertion during exercise is likely related to inspiratory muscle weakness. In athletes, perception of dyspnoea may be the limiting factor during high-intensity endurance exercise (Edwards and Walker, 2009). Whether this contributes to functional limitation in mobilising intensive care patients warrants investigation.

Thus the aim of this study was to answer the following questions:

1. In adult intensive care patients who have been recently weaned from 7 days or more of mechanical ventilation, is inspiratory muscle endurance impaired?
2. Is there a relationship between inspiratory muscle weakness, functional status and perceived exertion following successful ventilator weaning in this group?

METHOD

Design

This prospective observational study is a sub-study of a larger trial (Bissett et al., 2012d) of outcomes in intensive care patients ventilated for 7 days or longer. The present study analyses the baseline data collected for 43 participants eligible for inclusion in the post-weaning study between February 2011 and December 2013. The study was approved by the Australian Capital Territory Health Human Research Ethics Committee and patients provided their own written informed consent.

Setting

This prospective study occurred in a single tertiary 22 bed mixed medical / surgical intensive care unit in Canberra, Australia. This unit practices minimal sedation and early rehabilitation as the standard of care, whereby both nursing and physiotherapy staff facilitate sitting out of bed and mobilisation of patients as early as possible (in the absence of established contraindications)(Leditschke et al., 2012).

Participants

All patients ventilated for 7 days or longer were screened for inclusion in this study once successfully extubated for 48 hours. Patients were included if they were able to provide informed consent, were alert (Riker Sedation and Agitation Scale = 4)(Riker et al., 1999) and able to participate actively in inspiratory muscle training, and rate their dyspnoea via a modified Borg scale (Borg, 1982). Patients were excluded if they were <16 years of age, pregnant, had heart rates, respiratory rates, blood pressure or oxygen saturation outside stated limits, had active infection (Bissett et al 2012b) or were likely to be palliated imminently. Patients were also excluded from the study if they had participated in specific inspiratory muscle strengthening while ventilated. Figure 11 illustrates the flow of patients through the study. The most frequent reason for exclusion was impaired neurological status with an inability to follow commands (n=62).

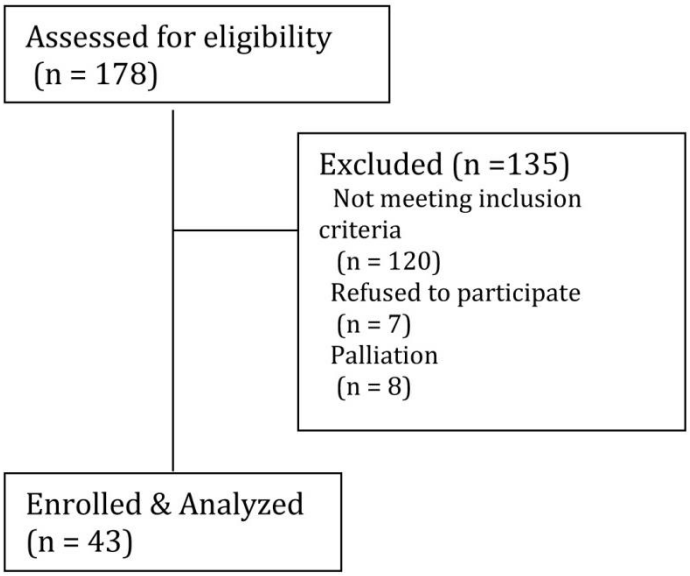


Figure 11: Flow of participants through Study 3

Variables and measures

The primary measure was inspiratory muscle endurance, measured as the Fatigue Resistance Index (FRI). Using the same protocol described previously by Chang and colleagues (Chang et al., 2005a), this test compares Maximum Inspiratory Pressures (MIP) before and after a 2 minute loading challenge, where patients breathe through a resistance of 30% of MIP. MIP is measured from residual volume using a handheld device (MicroRPM Respiratory Pressure Meter), in accordance with the protocol recommended by the American Thoracic Society and European Respiratory Society(Green et al., 2002). This requires patients to inhale maximally from residual volume, sustaining the effort for at least one second. Efforts are repeated three times to ensure less than 20% variability between measurements. This method of measuring MIP is both reliable and valid using portable handheld devices (Hamnegard et al., 1994). FRI is calculated as the post-challenge MIP divided by the pre-challenge MIP (scores <1.00 indicate the presence of fatigue).

The secondary measures include patients' rate of perceived exertion (RPE) using a modified Borg scale (0 – 10) (Borg, 1982) which has acceptable reliability and validity in intensive care unit patients (Powers and Bennett, 1999). Patients self-reported their RPE both at rest and during peak exercise. As peak exercise varied between patients (e.g. from sitting on the edge of the bed, to mobilising around the intensive care unit) depending on ability, patients were asked to report the highest exertion they experienced during any form of exercise on the day of measurement. All MIP, FRI and RPE measures were completed by specifically trained research staff.

Global function was measured by the treating physiotherapist using the Acute Care Index of Function (ACIF) tool(Scherer and Hammerich, 2008) which has good inter-rater reliability (Van Dillen and Roach, 1988) and construct validity (Roach and Van Dillen, 1988) in acute neurological patients.

Data analysis

Based on a previous study (Chang et al., 2005a), it was estimated that a sample size of 16 patients would be required to detect a change in 10% of MIP when measuring FRI (correlation co-efficient of >0.6). Normalized values for MIP scores were calculated using the method outlined by Evans and colleagues (Evans and Whitelaw, 2009). Parametric correlations were performed between variables, with statistical significance considered as $p<0.05$. Due to the skewed nature of the RPE data, non-parametric correlations were also calculated (Spearman's Rho) but results were consistent with parametric calculations and thus are not reported. All statistical analyses were performed using SPSS version 22.

RESULTS

Participants

The characteristics of the 43 patients (30 male, 13 female) included in the study are summarised in Table 6. The most common diagnosis in this cohort was pneumonia (n = 9) followed by sepsis (n=7) and multitrauma (n = 6). The mean duration of ventilation was 10.8 days (range 7 - 26 days) (seeTable 7), with most patients ventilated in spontaneous (pressure support) modes for the majority of their ventilation period (mean 8.9 days, range 1 – 24 days). The other 2 modes of ventilation used were synchronised intermittent mandatory ventilation (SIMV) and pressure control ventilation plus (PCV+). Sedation was used in all patients (predominantly propofol), with a mean sedation-free period of 4.8 days.

There was wide variability in functional level (ACIF scores), ranging from 8 to 92 (mean 40.3).

Table 6: Characteristics of participants in Study 3

AGE	SEX	DIAGNOSIS	APACHE II Scores	Duration of Ventilation (Days)	Spontaneous ventilation (PSV[1] only) days	SIMV[2]/PCV+[3] days	Sedation[4]	Sedation Free Days[5]	ACIF[6]
57	Male	Multitrauma	13	8	5	3	P, O, B	3	8
39	Male	Chest multitrauma	6	7	3	4	P	3	8
45	Male	Community acquired pneumonia	10	8	7	1	P, O, B	1	70
68	Male	Chest & pelvic trauma	18	7	6	1	P	0	17
52	Male	Multitrauma	22	11	6	5	O,B	6	17
81	Male	Hepatectomy	19	12	12	0	P, B	7	38
64	Male	Chest trauma	33	19	15	4	P, O, B	6	20
64	Female	Acute hepatic failure	40	7	3	4	P	4	60
69	Female	Middle cerebral artery CVA	27	10	10	0	P	2	60
43	Female	Sepsis	18	11	10	1	P, O	2	40
81	Female	Sepsis, pneumonia	17	8	7	1	P	7	37
81	Male	AAA Repair	14	9	6	3	P, O, B	7	34
66	Male	Chest multitrauma	20	11	10	1	P	9	47
60	Male	Septic shock	25	16	15	1	P, B	0	50
70	Male	Bacterial pneumonia	23	9	8	1	P, B, D	1	31
77	Female	Respiratory arrest	17	9	8	1	P	6	29
49	Female	Necrotizing fasciitis	21	9	7	2	P, B	0	16
55	Female	Status epilepticus	15	13	5	8	P, B	7	26
47	Male	Hospital Acquired pneumonia	25	9	8	1	P	8	49
67	Male	Bacterial pneumonia	16	22	21	1	P	17	50
43	Male	Hepatorenal syndrome	25	16	14	2	P, O	11	57
66	Female	Acute pulmonary oedema	16	9	8	1	P	7	20
49	Male	Left lung haematoma	17	16	13	3	P, B, D	2	20
85	Male	Hyponatraemia	33	8	7	1	P, B	5	92
63	Female	Bilateral pneumonia	29	9	9	0	P	5	40
63	Male	Bacterial meningitis	25	8	6	2	P, O, B, D	0	30
77	Male	Perforated duodenal ulcer	24	26	24	2	P	17	25
79	Male	Community acquired pneumonia	15	7	7	0	P	4	70
76	Male	Sepsis, pneumonia	12	8	8	0	P	6	40
61	Male	Vasculitis	10	7	7	0	P	6	70
85	Male	CABG	23	8	7	1	P	5	42
66	Male	Sepsis, multiple organ dysfunction	28	11	11	0	P	6	15
72	Male	Multifactorial respiratory failure	15	13	13	0	P	4	50
42	Female	Sepsis unclear origin	28	11	11	0	P, O	1	15
48	Male	Multiple organ failure	21	12	12	0	P	0	16
62	Male	Post CABG pleural effusions	24	10	7	3	P	7	56
80	Female	CABG	39	13	11	2	P	10	17
86	Male	Cardiogenic shock	31	13	10	3	P, B, D	0	58
41	Female	Exacerbation of Asthma	21	9	5	4	P, O, B, D	0	17
43	Female	Staph Aureus Bacteraemia	14	7	2	5	P	3	63
55	Male	Community acquired pneumonia	24	7	1	4	P	5	60
24	Male	Neutropaenic Respiratory Sepsis	16	10	7	3	P, O, B, D	2	64
48	Male	MVA Chest trauma	20	10	9	1	P, O, B	5	87

[1] PSV = Pressure Support Ventilation. [2] SIMV = Synchronised Intermittent Mandatory Ventilation. [3] PCV+ = Pressure Control Ventilation Plus. [4] Sedation: where P = Propofol, O = Opioid (eg Morphine), B = Benzodiazepines, D = Dexmedetomidine (recorded as any dose delivered on any day). [5] Sedation free days - full days where no sedation of any kind was administered during the ventilation period. [6] ACIF = Acute Care Index of Function (score / 100).

Table 7: Characteristics of participants and summary of measures in Study 3

	Mean	*Standard Deviation*	*Range*
Age (years)	61.6	15.17	24 - 86
Apache II Score (Admission)	21.1	7.45	6 - 40
Total duration of ventilation (days)	10.8	4.11	7 - 26
Pressure Support Ventilation (days)	8.9	4.48	1 - 24
Sedation-free period (days)	4.8	4.01	0 - 17
Acute Care Index of Function (score / 100)	40.3	21.7	8 - 92
Maximum Inspiratory Pressure (cm H_2O)	34.2	19.4	6 - 87
Maximum Inspiratory Pressure (% predicted)	38.6	19.7	6 - 86
Fatigue Resistance Index (FRI)	0.90	0.32	0.21 – 2.00
Rate of Perceived Exertion (Rest) (score / 10)	1.95	2.78	0 - 9
Rate of Perceived Exertion (Exercise) (score / 10)	3.40	3.50	0-10

While the mean FRI was below 1.0 (0.90, SD 0.319), there was considerable spread in the sample (Figure 12), such that 15 (37%) of patients scored less than 0.80, while 4 (10%) scored above 1.20, including one notable outlier at 2.0.

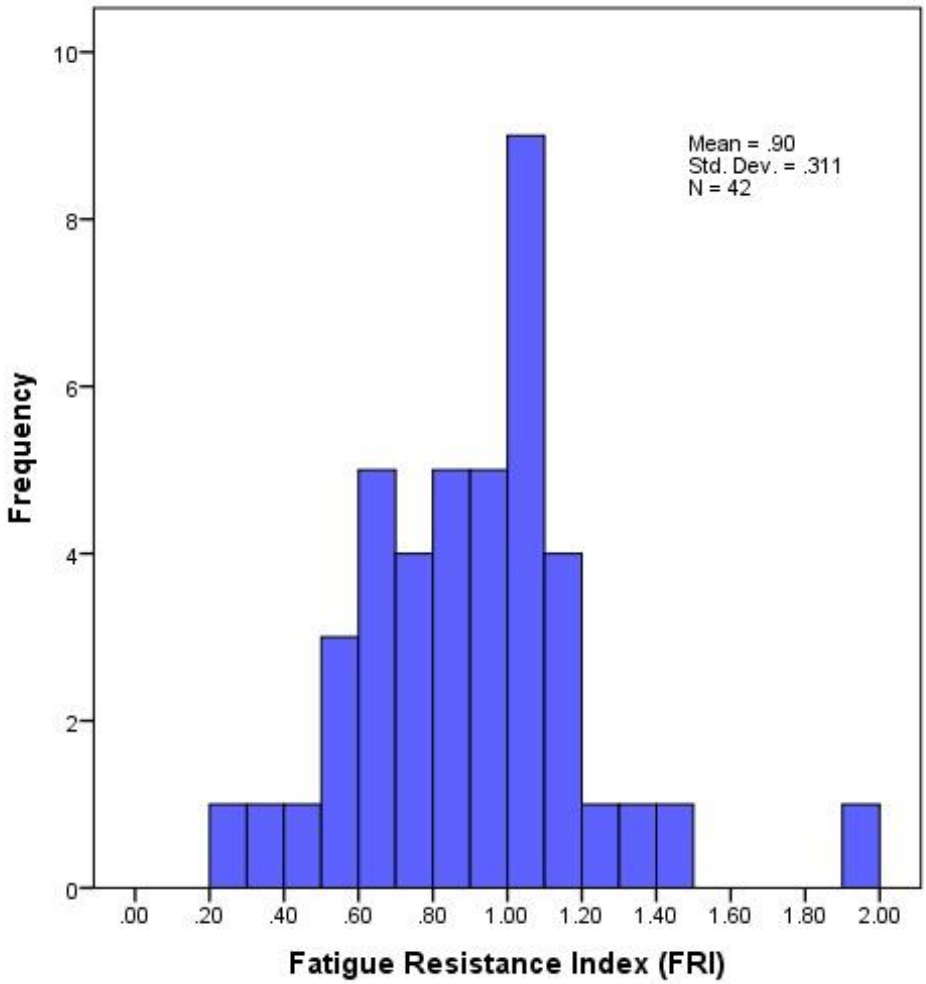


Figure 12: Frequency distribution of fatigue resistance index, where scores below 1.0 indicate a drop in strength after an endurance challenge

There was also wide variability in MIP scores (Figure 13), with one patient scoring 86% of their predicted MIP (87). This patient had an FRI of 1.06, i.e. no evidence of fatigability. In contrast, the patient with the lowest MIP score (6) had an FRI of 0.33, indicating severely impaired fatigue resistance. MIP was significantly positively correlated with FRI (r = 0.39, p = 0.01).

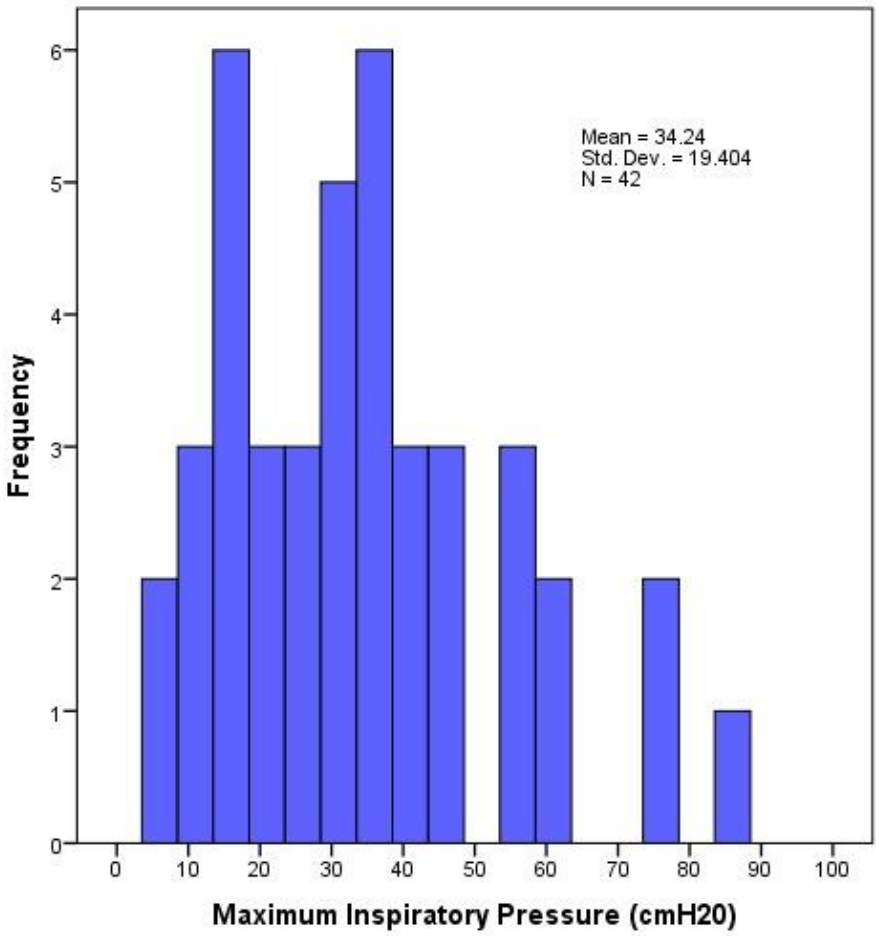
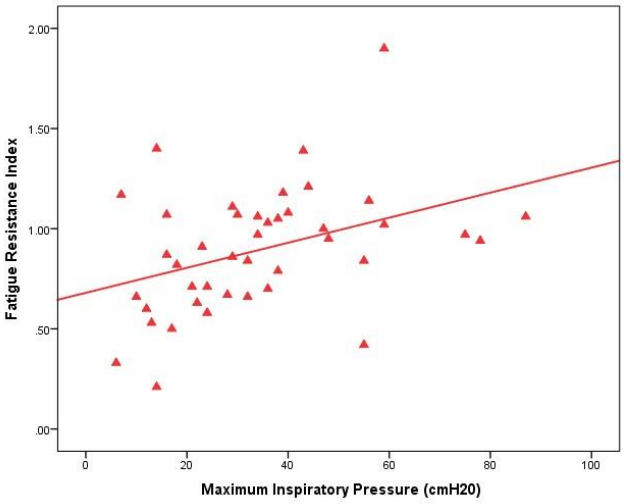


Figure 13: Frequency distribution of maximum inspiratory pressure (cm H_2O)

There was a weak positive trend (see Figure 14b), but no significant correlation between MIP scores and functional (ACIF) scores (r = 0.243, p = 0.121).

a)



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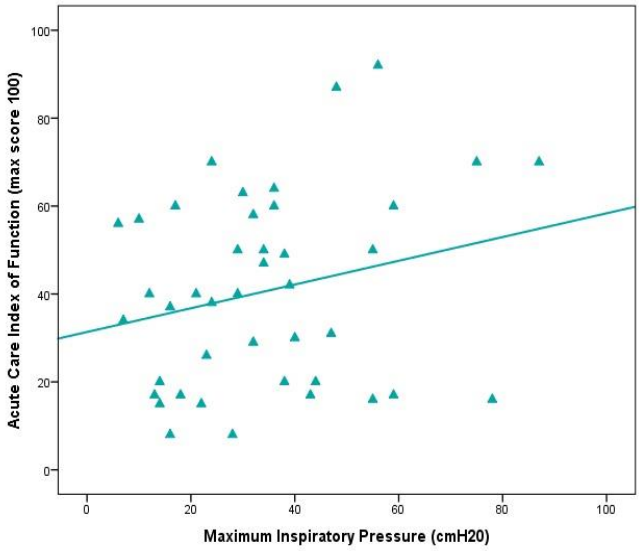

c)

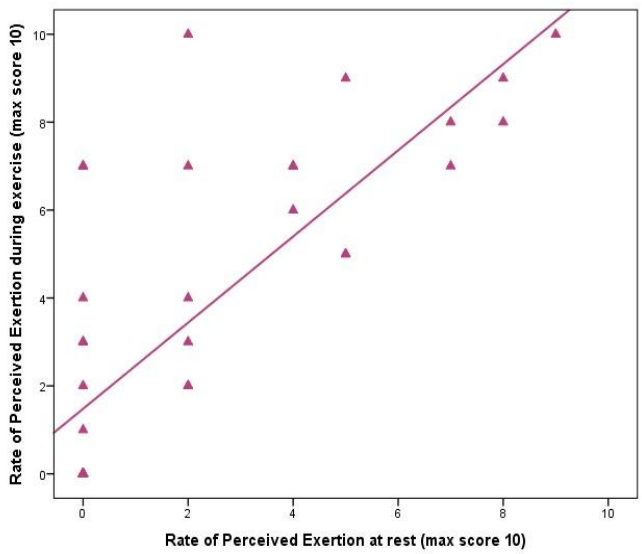

Figure 14: Correlations between measures: a) between MIP (cm H_2O) and FRI scores. b) between MIP (cm H_2O) and ACIF scores. c) between RPE scores at rest and during exercise.

Of the 43 patients, 17 (40%) reported an RPE greater than zero at rest. While RPE at rest was strongly correlated with RPE during exercise (r = 0.78, p <0.01)(Figure 14c), there were no significant correlations between RPE and ACIF, MIP or FRI (see Table 3). Duration of ventilation and APACHE II scores were not correlated with ACIF, MIP or FRI (Table 8).

Table 8: Correlations between variables in Study 3 (Pearson r)

	ACIF	*MIP*	*FRI*
RPE (Rest)	r= -0.17	r= -0.18	r= -0.12
	p= 0.28	p= 0.27	p= 0.46
RPE (Exercise)	r= -0.11	r= -0.15	r= -0.14
	p= 0.95	p= 0.37	p= 0.39
APACHE II	r= 0.05	r= -0.12	r= -0.79
	p= 0.77	p= 0.44	p= 0.62
Duration of	r= -0.10	r= -0.45	r= -0.20
ventilation	p= 0.51	p= 0.77	p= 0.20

DISCUSSION

The results of this study provide further evidence that inspiratory muscle endurance is often impaired in intensive care patients who have been recently weaned from mechanical ventilation of at least 7 days duration, even if the patients have been ventilated predominantly with spontaneous modes (e.g. pressure support). However there does not appear to be a close relationship between inspiratory muscle weakness and either function or perceived exertion in this cohort.

Our findings regarding impaired fatigue resistance (FRI 0.90) within 48 hours of weaning from mechanical ventilation are consistent with previous findings (Chang et al., 2005a). Chang and colleagues demonstrated a mean FRI of 0.88 in a group of 20 participants who had been ventilated for a mean of 4.6 days and were followed up on average 7 days (range 2 – 16) following weaning. The consistency in the magnitude of the observed FRI deficit suggests that impairments in FRI may be mostly attributable to changes that occur within the first few days of ventilation, rather than following weaning. This early change would be consistent with clinical studies showing proteolysis occurring within 69 hours of controlled ventilation (Levine et al., 2008) and recent physiological studies demonstrating reduced muscle fibre cross-sectional area and reduced protein to DNA ratios (29%) in skeletal muscles within the first 3 days of intensive care admission (Puthucheary et al., 2013).

However, the fact that the relatively longer duration of ventilation in our group (mean 10.5 days) did not result in lower FRI scores is in contrast with the finding by Chang et al that FRI is negatively correlated with duration of ventilation ($r = -0.65$, $p = 0.007$). In the present study there was only a non-significant negative association between FRI and duration of ventilation ($r = -0.20$, $p = 0.20$). This may be explained by the predominance of spontaneous modes (e.g. pressure-support ventilation) used in the current study (see Table 6), whereas patients in Chang's cohort were predominantly ventilated using controlled methods.

It is not surprising that RPE scores at rest were strongly correlated with RPE scores during exercise. A patient feeling short of breath at rest is highly likely to feel more exertional distress when they exercise as the metabolic demand for oxygen increases. In this study, 40% of patients reported an RPE greater than zero at rest indicating an elevated work of breathing. However it was unexpected that RPE scores were only weakly correlated with fatigue resistance or functional scores, as it was expected that poor inspiratory fatigue resistance would manifest as increased perceived exertion as the work of breathing increases during exercise. It is possible that some participants have difficulty using the Modified Borg Scale to rate their perceived exertion and dyspnoea, or that the scale is insufficiently sensitive to detect relationships at this level. However to our knowledge there is no other readily available standardised tool to measure perceived exertion or dyspnoea in this context. The development of a sensitive standardised tool to measure exertion in critically unwell patients could be helpful in future.

The lack of correlation between MIP and function could also partly be explained by deficits in motor control. While inactivity leads to early muscle proteolysis, it is highly likely that inactivity also affects neural programming. In studies of specific inspiratory muscle training, early apparent improvements in MIP scores (e.g. within 2 weeks of training) could be attributed to more efficient motor programming (Huang et al., 2003) rather than muscle hypertrophy. Thus it is likely that there is not a simple linear relationship between strength and function, and neural factors should be considered in future studies.

As 60% of patients in this study rated their perceived exertion as zero during exercise, it is also possible that 'peak exercise' (e.g. mobilisation with assistance away from the bed space) was of insufficient intensity to challenge inspiratory muscles. If these recently weaned patients do not perceive any raised exertion, the training intensity may be inadequate. Even in an intensive care unit where early mobilisation is the standard of care, we may be yet to determine the limitations of exercise in the critically ill. However, the patient's perceived exertion is likely to be an important determinant of exercise capacity. In athletes working at peak exercise, exercise performance can be limited by the perception of exertion, even in the absence of peripheral biomarkers of fatigue (Edwards and Walker, 2009). The evidence that this perception of exertion is modifiable in athletes with training of the respiratory muscles may also have implications for recently weaned intensive care patients. It is possible that the 37% of patients demonstrating reduced FRI in this study may benefit from targeted training of their inspiratory muscles. inspiratory muscle training can hasten weaning in older intensive care patients (Cader et al., 2010) but to our knowledge this remains uninvestigated in the post-weaning period. This is an important area of future research.

The limitations of this study include the fact that these results may be valid only for intensive care patients who have been weaned in a unit where minimal sedation and early mobilisation are the norm. It is plausible that FRI, MIP and ACIF scores would differ considerably in patients undergoing deep sedation and bed rest as early deep sedation independently delays extubation and increases mortality (Shehabi et al., 2012). Furthermore, the failure to find correlations between these variables may be attributable to the relatively small sample size, although this study was larger than previous studies (Chang et al., 2005a).

Despite these limitations, the consistency of the primary measure (FRI) with previous studies confirms that impaired fatigue resistance is detectable in at least a third of intensive care patients within the first few days following weaning. These results have implications for all clinicians working with intensive care patients in the immediate post-weaning period. Medical and nursing staff can reassure patients that it is common to experience raised perceived exertion following weaning, even at rest, as this is a foreseeable consequence of prolonged mechanical ventilation. As dyspnoea is complex and multifactorial in weaning from mechanical ventilation (Bissett et al., 2012a), the psychological benefits of acknowledgement and reassurance may be important for the patient's experience.

Furthermore, clinicians should be aware that recently weaned patients may report high RPE levels during exercise, particularly if RPE is raised at rest. However, in our experience, raised RPE is not necessarily a barrier to participation in early rehabilitation in intensive care and physiotherapists and nurses can work together to optimise patients' exercise capacity even in the presence of inspiratory muscle weakness.

In conclusion, in intensive care patients recently weaned from mechanical ventilation of duration 7 days or longer, impaired respiratory endurance is detectable in one third of patients. Impaired respiratory muscle endurance is associated with inspiratory muscle weakness. Inspiratory muscle weakness does not appear to be closely associated with functional measures or perceived exertion 48 hours following successful weaning in an intensive care unit where early mobilisation and minimal sedation are the standard of care.

CHAPTER 5: Study 4

Inspiratory Muscle Training to Hasten Recovery from Mechanical Ventilation: A Randomised Trial

This chapter has been accepted as an original research publication in the peer-reviewed journal Thorax and is currently in press.

INTRODUCTION

Invasive mechanical ventilation causes respiratory muscle weakness in intensive care unit (ICU) patients(Levine et al., 2008). After 18 to 69 hours of controlled mechanical ventilation, diaphragm proteolysis and atrophy occurs(Levine et al., 2008) and respiratory muscle weakness has been observed both while patients are mechanically ventilated(De Jonghe et al., 2007) and following successful extubation(Chang et al., 2005a, Bissett et al., 2015b). Persistent respiratory muscle weakness may contribute to the residual dyspnoea(Bissett et al., 2015b), impaired physical function(Iwashyna et al., 2010, Bissett et al., 2015b) and poor quality of life(Cuthbertson et al., 2010) observed in ICU survivors.

Inspiratory muscle training (IMT) is a relatively novel training strategy to improve inspiratory muscle strength in intensive care patients. Threshold-based IMT is performed using a handheld device which provides carefully titrated constant resistance on inspiration only. A pre-set threshold level of pressure is required to open a one-way valve and allow inspiratory flow, which is important in ensuring accurate titration of resistance as some other IMT devices are flow-dependent which means the resistance varies with patient effort. Using a threshold IMT device the level of inspiratory pressure required to open the valve is increased over time to provide an ongoing training load as the patient's inspiratory muscles become stronger. IMT improves respiratory muscle strength in patients undergoing invasive mechanical ventilation(Bissett and Leditschke, 2007, Cader et al., 2010, Martin et al., 2002, Martin et al., 2011, Condessa et al., 2013) and a recent systematic review suggested that IMT performed prior to extubation enhances weaning success, although it does not appear to reduce rates of reintubation or likelihood of survival(Elkins and Dentice, 2015).

However, participation in threshold-based IMT while mechanically ventilated requires patients to be alert and cooperative with training(Bissett et al., 2012b). For many reasons, intensive care patients may not be suitable candidates for IMT whilst ventilator-dependent (e.g. due to sedation or delirium) and may only have sufficient cognitive capacity to participate in training once weaned from mechanical ventilation. Although case studies have shown improvements in inspiratory muscle strength with IMT(Chang et al., 2005b), there have been no randomised trials of IMT in intensive care patients in the post-extubation period.

As residual inspiratory muscle impairment has been demonstrated in intensive care survivors ventilated for 7 days or longer(Chang et al., 2005a, Bissett et al., 2015b), we conducted a randomised trial to establish the effects of post-extubation IMT in a heterogeneous sample of intensive care patients who had been invasively ventilated for at least 7 days. Primary endpoints included inspiratory muscle strength and endurance following 2 weeks of training. This 2 week time frame was selected pragmatically, as pilot data indicated that most intensive care survivors remained inpatients during this 2 week period and would receive supervised physiotherapy. To date, no studies of IMT in intensive care patients have included patient-centred outcomes or rates of readmission to ICU. Therefore secondary endpoints included health-related quality of life, dyspnoea and functional levels after 2 weeks of training. Post-intensive care length of stay, rate of intensive care readmission and in-hospital mortality were also explored. We hypothesized that in the IMT group, improvements in inspiratory muscle strength and fatigue resistance would lead to reduced dyspnoea, improved quality of life and physical function, and lower rates of intensive care readmission and in-hospital mortality compared to the control group(Bissett et al., 2012d) .

MATERIALS AND METHODS

Design

We conducted a single-centre randomised trial with concealed allocation (computer-generated random-number sequence, managed by off-site administrative staff and obtained via telephone by the chief investigator following enrolment), assessor-blinding and intention to treat analysis (Bissett et al., 2012d). The study was approved by the Australian Capital Territory Health Human Research Ethics Committee and the University of Queensland Medical Research Ethics Committee, and the published study protocol(Bissett et al., 2012d) (trial registration ACTRN12610001089022) complied with the CONSORT guidelines for clinical trials(Moher et al., 2001).

Participants, therapists, centre

All patients invasively mechanically ventilated for 7 days or longer were screened for eligibility. Patients were deemed eligible if they had been successfully weaned from mechanical ventilation (>48 hours), and within the 7 days following successful weaning they met the inclusion criteria (aged ≥ 16 years, able to provide informed consent, and alert and able to participate in training with a Riker(Riker et al., 1999) score of 4). Patients

were excluded if they had participated in inspiratory muscle training while mechanically ventilated, declined to participate, were pregnant, were not alert or able to participate with training, were experiencing significant pain or distress that interfered with breathing capacity, were deemed medically unstable or for palliation (i.e. death likely in the next few weeks). Based on *a priori* power calculations, a total of 70 participants was required to detect a 0.10 change in the primary outcome measures with a power of 0.80 (inflating group size by 15% to allow for known mortality of 12.8%(Bissett et al., 2012d)). Although the minimal clinically important difference in MIP scores has not been established in this patient group, the 0.10 change level was selected based on previous studies of inspiratory muscle strength and fatigue resistance in intensive care survivors(Chang et al., 2005a, Chang et al., 2005b) to allow comparisons to be drawn between studies. All participants provided informed written consent to participate in the study.

Training was supervised by registered physiotherapists specifically trained in delivering inspiratory muscle training as described in our previously published protocols(Bissett et al., 2012b, Bissett et al., 2012d). Therapists could not be blinded to group allocation. The study was conducted in an Australian tertiary hospital (Canberra Hospital) where usual intensive care practice includes minimal sedation and early proactive mobilisation(Leditschke et al., 2012). A second site was also included (Calvary Hospital), however no patients were recruited from this site due to failure to meet eligibility requirements.

Intervention

Participants were randomised to receive either usual care (control group) or inspiratory muscle training in addition to usual care (IMT group) for 2 weeks following enrolment. Usual care physiotherapy included an individually tailored and supervised program of interventions which included any of the following: assisted mobilisation, secretion clearance treatments including positive expiratory pressure techniques, deep breathing exercises without a resistance device and upper and lower limb exercises.

IMT was performed using the Threshold IMT inspiratory muscle trainer (Threshold IMT device HS730, Respironics NJ, USA). This device was used with the mouthpiece, or a flexible connector if required to attach to a tracheostomy (Figure 15). Where a tracheostomy remained in situ, IMT was always performed with the cuff inflated to ensure accurate loading. The physiotherapist prescribed an intensity of 50% of MIP for the first

training set, but then quickly increased this to the highest tolerable intensity that allowed the participant to just complete the 6th breath in a set of 6 breaths, with 5 sets of 6 breaths completed each session. Patients were allowed to rest between sets until they felt ready to commence the next set, which was typically less than 1 minute of resting. The intensity was increased daily by the physiotherapist across the training period to provide an adequate training stimulus. This was achieved by manually increasing the threshold resistance by 1-2cm H_2O until the participant could only just open the poppet valve on the 6th breath in each set. Training commenced on the day of enrolment and continued once daily (weekdays only) for 2 weeks. A sham device was not used for comparison as previous studies of IMT have found the sham device may provide a training effect in participants with very low baseline strength(Cheah et al., 2009).

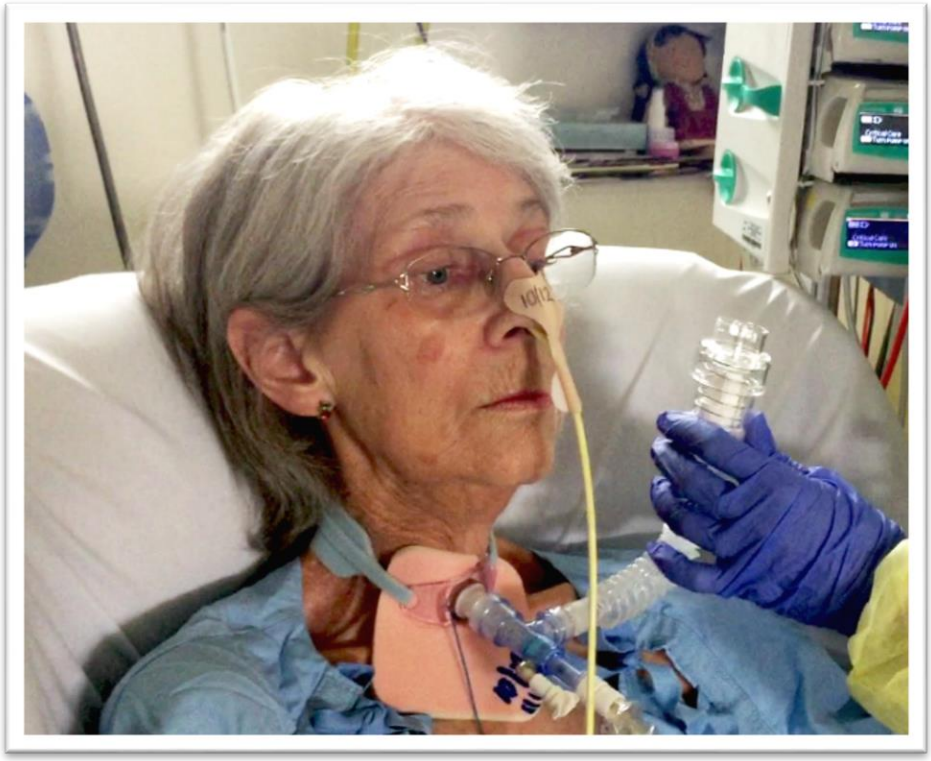

Figure 15: Inspiratory muscle training via a tracheostomy.
Note the flexible tubing connecting the inspiratory muscle trainer to the closed suction device.

Measures

Primary endpoints:

Measures of inspiratory muscle performance were recorded on enrolment and at the end of the intervention period 2 weeks later by 6 specifically-trained research nurses blinded to group allocation. Inspiratory muscle strength was assessed as maximum inspiratory pressure (MIP), measured as previously described(Bissett et al., 2012d) using a portable MicroRPM Respiratory Pressure meter (CareFusion, San Diego, USA) in accordance with the protocol described by the American Thoracic Society and European Respiratory Society(Green et al., 2002). This device has been shown to have excellent reliability in measuring MIP in non-ventilated participants (ICC 0.83-0.90)(Dimitriadis et al., 2011). Raw MIP scores were normalised using the method described by Evans et al(Evans and Whitelaw, 2009) and have been presented as percentage of predicted values to account for known variation of MIP with age and gender. Inspiratory muscle fatigue was measured using the fatigue-resistance index (FRI) technique described by Chang and colleagues(Chang et al., 2005a), based on the Maximum Incremental Threshold Loading test described in the American Thoracic Society / European Respiratory Society guidelines(Clanton et al., 2002).The pre-specified endpoint was the between-group difference in change in outcome measures (i.e. the change from enrolment to 2 week follow-up values).

Secondary endpoints:

Measures of quality of life, dyspnoea and physical function were completed on enrolment and 2 weeks later. Quality of Life was measured using the SF-36v2 tool (acute 1 week time frame) (under license QualityMetric USA) and the EQ-5D-3L tool (under license EuroQol International). These tools were administered by research nurses blinded to group allocation. The SF-36 tool has demonstrated reliability, responsiveness, construct and criterion validity and is responsive to clinical improvement in an intensive care population(Hayes et al., 2000). The EQ-5D-3L tool has also been used in intensive care patient follow-up(Granja et al., 2003) and is likely to give a more general measure of health-related quality of life than the SF-36.

Dyspnoea was measured using a Modified Borg Dyspnoea scale, where dyspnoea is a patient-reported categorical score out of 10, which has acceptable reliability and validity in patients undergoing mechanical ventilation(Powers and Bennett, 1999). Dyspnoea was recorded both at rest (sitting comfortably in the chair or bed) and during exercise (the peak

exercise activity experienced in the previous 24 hours) by research nurses blinded to group allocation.

Functional level including mental status, bed mobility, transfers and mobility, was assessed using the Acute Care Index of Function (ACIF)(Roach and Van Dillen, 1988) which has excellent inter-rater reliability in intensive care patients(Bissett et al., 2015a). Scores on enrolment were completed by physiotherapists blinded to group allocation, however follow-up ACIF scores were recorded by the treating physiotherapist who was not blinded to group allocation.

Other secondary endpoints included rate of intensive care unit readmission, requirement for reintubation, post-ICU hospital length of stay and in-hospital mortality. These data were extracted from hospital databases by research nurses blinded to group allocation. Post-hoc analysis of participants who died during the hospital admission included retrospective calculation of the risk of death based on acute physiology and chronic health evaluation (APACHE II) scores.

Data analysis

The intent-to-treat (ITT) population was defined as all 70 randomised participants. The per-protocol population was defined as all participants with both enrolment and 2 week follow-up data. All analyses were repeated in both the ITT and per-protocol populations. Paired t-tests were used to compare within group differences. Mixed linear models were used to assess the between-group difference of the changes between enrolment and follow-up measures, including age and APACHEII scores as covariates. Diagnostic plots (predicted means versus Pearson's residuals) were generated to assess model assumptions. Mortality data were analysed using chi square and Fisher’s exact test. Statistical significance was set as $p<0.05$. All analyses were done using SPSS version 21.

RESULTS

Flow of participants through the study

The flow of participants is presented in Figure 16. Between February 2011 and August 2015, 70 participants were recruited to participate in the study with 34 allocated to the IMT group and 36 to the control group. Participant characteristics are presented in Table 9 and are similar between IMT and control groups, except for a higher percentage of male participants in the IMT group (71 vs 58%).

The most frequent reason for exclusion from the study was poor neurological status with resultant inability to provide consent. Six participants were lost to follow-up in each group, most commonly due to transfer to another hospital within the study period. Two participants died within the intervention period, both in the IMT group. Two participants died after the intervention but prior to hospital discharge, both in the IMT group. Thus the total mortality in the treatment group was 12%, compared to 0% in the control group. Where patients were lost to follow-up regarding the primary outcome measures, other post-intervention secondary measures were still obtained through hospital databases (Table 12).

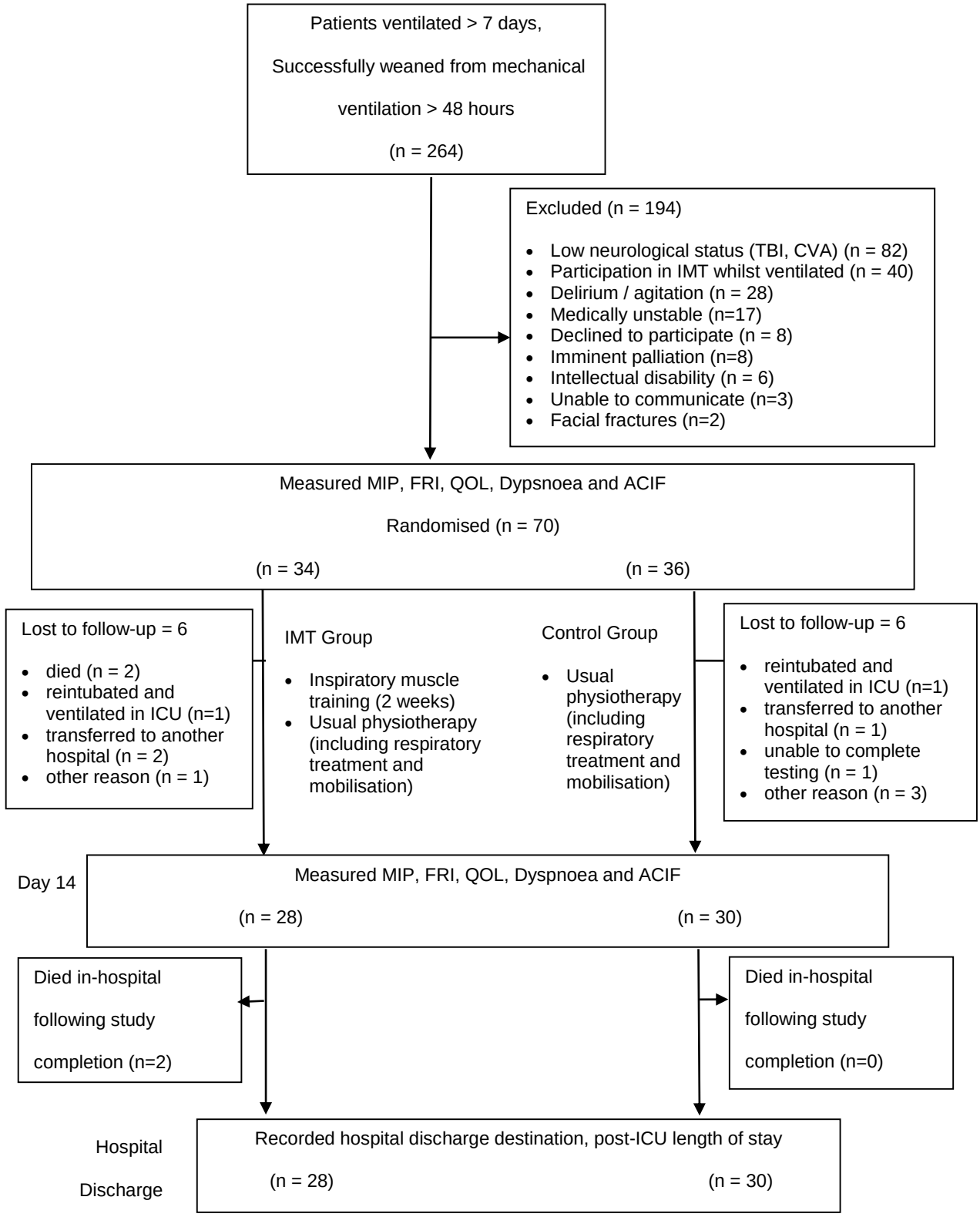

Figure 16: Flow of participants through Study 4

Table 9: Characteristics of Participants in Study 4

Characteristic	Randomised (n = 70)		Lost to follow-up (n = 12)	
	IMT (n = 34)	Control (n = 36)	IMT (n = 6)	Control (n = 6)
Age *(yr)*, mean (SD)	59 (16)	59 (13)	67 (11)	50 (10)
Gender, n males (%)	24 (71)	21 (58)	4 (67)	2 (33)
Diagnosis, n (%)				
Sepsis	4 (12)	9 (25)	0 (0)	1 (17)
Pneumonia	4 (12)	7 (19)	0 (0)	0 (0)
Multitrauma	6 (18)	8 (22)	0 (0)	2 (33)
CVA	1 (3)	1 (3)	0 (0)	0 (0)
Respiratory Failure	4 (12)	1 (3)	0 (0)	0 (0)
Cardiothoracic Surgery	1 (3)	1 (3)	2 (33)	0 (0)
Abdominal Surgery	3 (9)	1 (3)	2 (33)	0 (0)
Encephalopathy / Seizures	3 (9)	4 (11)	1 (17)	1 (17)
Other	8 (24)	4 (11)	1 (17)	2 (33)
APACHE II scores, mean (SD)	20.1 (7.8)	22.9 (8.3)	23.5 (9.0)	19.3 (12.0)
Highest SOFA score, mean (SD)	7 (4)	8 (4)	4 (2)	7 (5)
Length of ICU stay *(days)*, mean (SD)	15 (6)	13 (8)	20 (7)	9 (1)
Total duration of ventilation *(days)*, mean (SD)	11 (4)	10 (2)	14 (7)	8 (1)
Duration of PSV *(days)*, mean (SD)	10 (4)	9 (3)	12 (7)	7 (1)

IMT = Inspiratory Muscle Training group, CVA = cerebrovascular accident, APACHE II = acute physiology and chronic health evaluation score; SOFA = sequential organ failure assessment score; ICU = intensive care unit, PSV = pressure support ventilation; SD = standard deviation.

Compliance with trial protocol

In the IMT group, across the 34 participants, 85% of all intended IMT treatments (potential 10 treatments for each patient) were completed. 23 participants (67%) completed more than 90% of the prescribed IMT sessions, while 2 (6%) participants completed 20% or less of the prescribed IMT sessions. The most frequent reason for lack of completion was participant refusal due to generalised fatigue. IMT was generally well-tolerated and no adverse effects were reported during or immediately after training in any participant. No participants in the control group inadvertently received inspiratory muscle training. Two participants (both in the control group) were discharged home prior to completion of the two week intervention period, however they attended the outpatient department for completion of outcome measures.

Effect of intervention

The intention-to-treat and per-protocol analyses yielded entirely congruent results, therefore only the intention-to-treat analysis is presented. Changes in outcome measures within and between groups are summarized in Table 10 and Table 11. MIP improved in both groups, with a statistically significant greater increase in the IMT group than the control group (17% in IMT group vs 6% in control, p = 0.024) (Figure 17a). No statistically significant change in FRI was observed for either group at the end of the study period (0.03 vs 0.02, p=0.81) (Figure 17b).

Table 10: Comparisons within groups for outcome measures in Study 4

OUTCOME	GROUPS			
	Week 0 Estimated Marginal Mean (SEM)		*Week 2* Estimated Marginal Mean (SEM)	
	IMT (n = 34)	Control (n = 36)	IMT (n = 34)	Control (n = 36)
MIP % predicted	44 (5)	40 (5)	61*** (5)	47* (5)
Fatigue resistance index / 1.00	0.86 (0.05)	0.96 (0.05)	0.89 (0.05)	0.98 (0.05)
QOL: SF-36	0.43 (0.02)	0.47 (0.02)	0.51** (0.02)	0.51 (0.02)
QOL: EQ5D	41 (4)	51 (4)	55** (4)	53 (4)
ACIF /1.00	0.36 (0.04)	0.43 (0.04)	0.61*** (0.04)	0.68*** (0.04)
RPE rest /10	2.0 (0.4)	1.3 (0.4)	1.1 (0.4)	0.9 (0.4)
RPE exercise /10	3.2 (0.5)	2.4 (0.5)	2.7 (0.5)	2.6 (0.5)

SEM = standard error of the mean, IMT = Inspiratory Muscle Training group, MIP = maximum inspiratory pressure, QOL = Quality of Life (SF-36 or EQ5D tools), ACIF = Acute Care Index of Function, RPE = rate of perceived exertion. * = $p < 0.05$. ** = $p < 0.01$. *** = $p < 0.001$.

Table 11: Differences within and between groups for each outcome measure at 2 weeks in Study 4

Outcome	Differences within groups		Differences between groups (Mixed Model Analysis)	
	Week 2 minus Week 0 Mean (SEM)			
	IMT (n = 34)	Control (n = 36)	Difference between groups (95% confidence interval)	p value
MIP % predicted	17 (4)	6 (3)	11 (2 to 20)	p=0.024*
Fatigue resistance index / 1.00	0.03 (0.05)	0.02 (0.5)	0.02 (-0.15 to 0.12)	p=0.816
QOL: SF-36	0.08 (0.02)	0.04 (0.02)	0.05 (-0.01 to 0.10)	p=0.123
QOL: EQ5D	14 (4)	2 (4)	12 (1 to 23)	p=0.034*
ACIF /1.00	0.25 (0.04)	0.25 (0.04)	0.00 (-0.12 to 0.12)	p=0.974
RPE rest /10	-0.8 (0.4)	-0.4 (0.4)	-0.4 (-1.5 to 0.7)	p=0.483
RPE exercise /10	-0.5 (0.4)	0.2 (0.4)	- 0.7 (-1.8 to 0.4)	p=0.223

SEM = standard error of the mean, IMT = Inspiratory Muscle Training group, QOL = Quality of Life (SF-36 or EQ5D tools), ACIF = Acute Care Index of Function, RPE = rate of perceived exertion. * = p <0.05. ** = p < 0.01. *** = p < 0.001. All analyses are intention-to-treat.

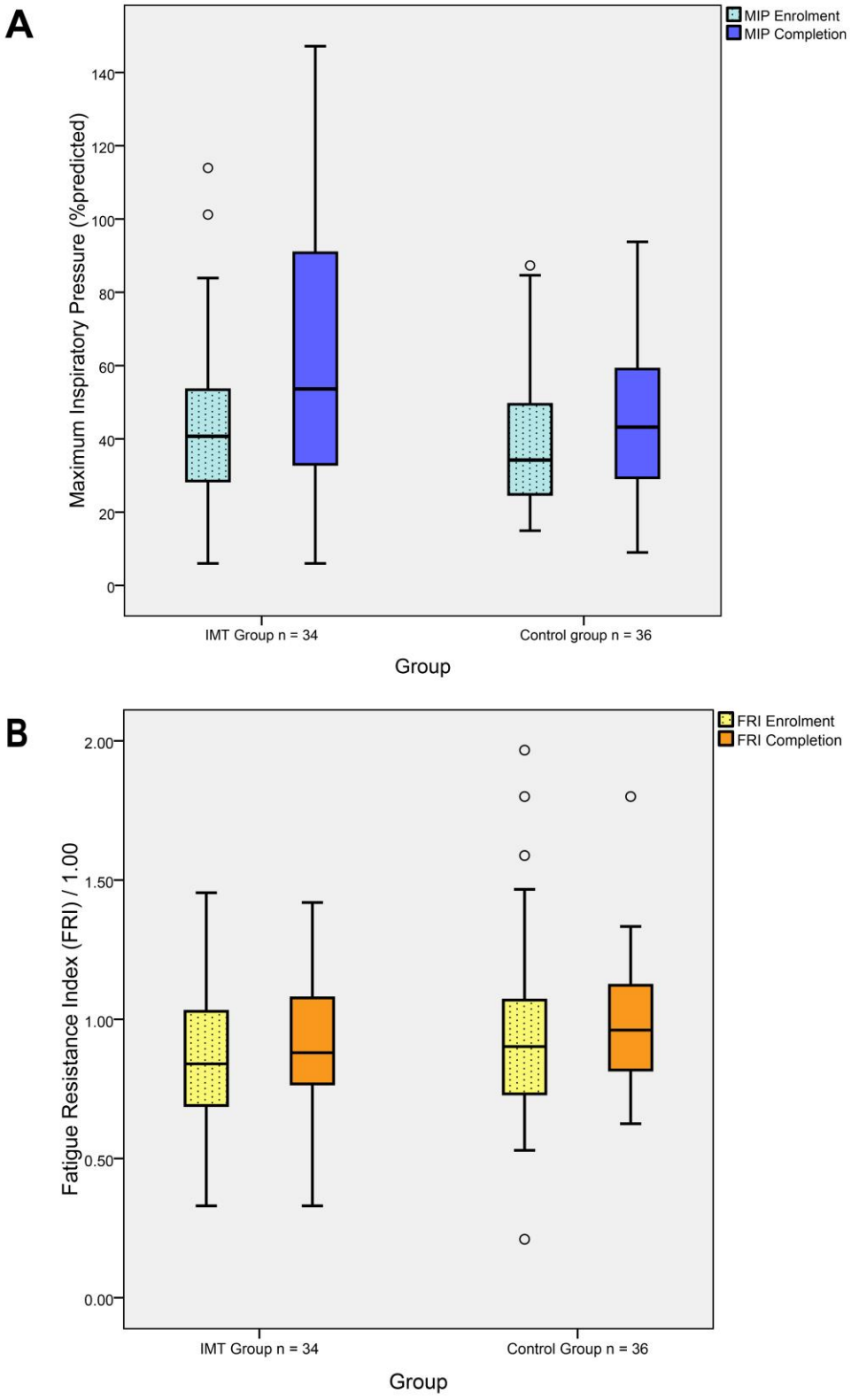

Figure 17: Inspiratory muscle changes in both groups in Study 4

Inspiratory muscle changes in both groups: A) Changes in Maximum Inspiratory Pressure scores pre and post intervention, B) Changes in Fatigue Resistance Index pre and post intervention. The box is drawn from the 25th percentile to the 75th percentile, the whiskers are drawn at 1.5 times inter-quartile range, with outliers represented with dots.

Both quality of life measures demonstrated statistically significant improvements from baseline in the IMT group only (mean difference = 14, p = 0.001 for EQ5D; mean difference = 0.08, p = 0.001 for SF-36) (Figure 18a and Figure 18b). Between groups, the difference in EQ5D scores was higher in the IMT group (14 vs 2, p=0.034). There was no statistically significant difference in SF-36 scores, although the point estimates suggested a potential benefit (mean difference = 0.05, 95% CI = -0.01 – 0.10).

Both groups demonstrated significant improvements in functional outcomes, as measured by the ACIF (Figure 18c); however, these improvements did not differ between groups (0.25 vs 0.25, p=0.974). Changes in dyspnoea scores both at rest and during exercise were not statistically significant either within or between groups across the intervention period.

There were no significant differences between groups for post-ICU length of stay, reintubation rate or ICU readmission (Table 12). However in-hospital mortality was higher in the IMT group (p=0.051) with 4 deaths, 2 during the 2 week intervention period and 2 following the intervention period (Table 13).

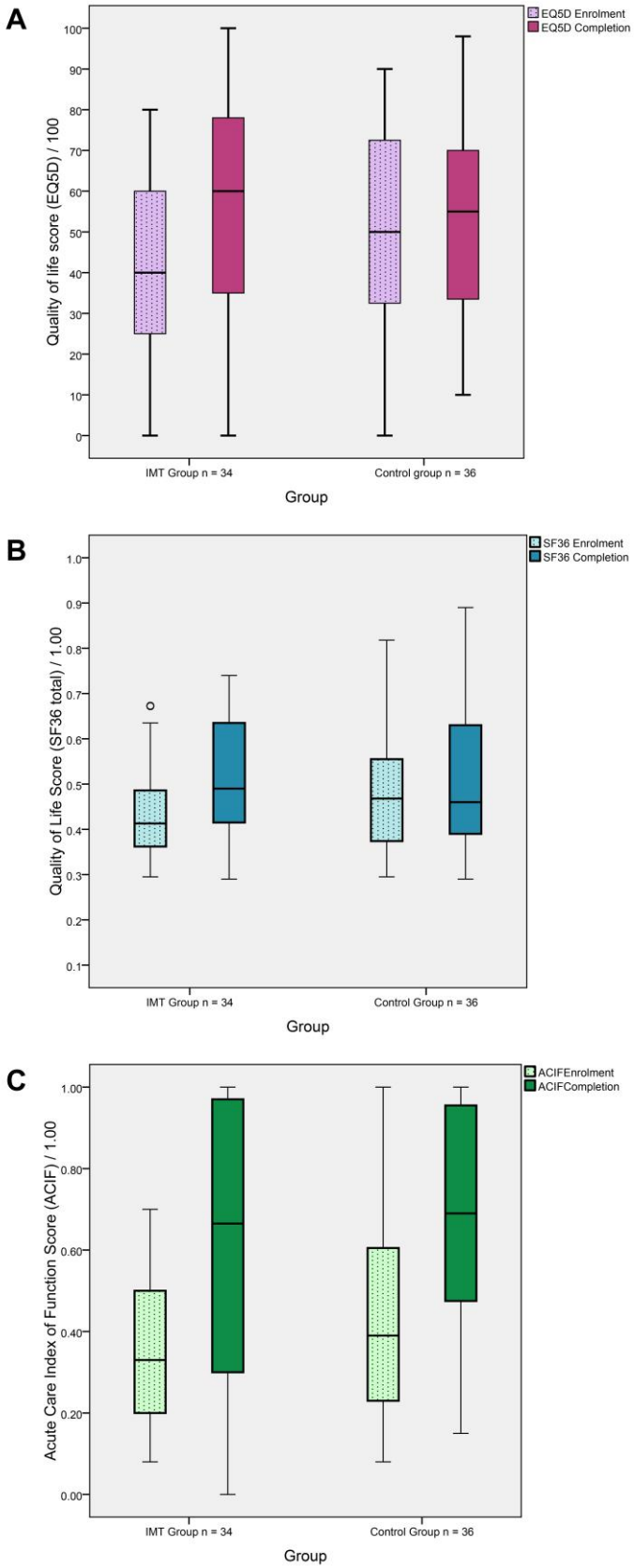

Figure 18: Quality of life and functional measures in both groups in Study 4

Quality of life and functional measures in both groups: a) Changes in EQ5D scores pre and post intervention, b) Changes in SF36 scores pre and post intervention, c) Changes in Acute Care Index of Function pre and post intervention. The box is drawn from the 25th percentile to the 75th percentile, the whiskers are drawn at 1.5 times interquartile range, with outliers represented with dots.

Table 12: Comparisons between groups for post-intervention outcome measures in Study 4

Outcome	Randomized (n = 70)	
	IMT (n = 34)	Control (n = 36)
Post-ICU hospital length of stay, mean (SEM)	35 (8)	37 (9)
Number of participants re-admitted to ICU, n (%)	6 (18)	8 (22)
Number of participants re-intubated, n (%)	6 (18)	8 (22)
In-hospital mortality,n (%)	4 (12)[#]	0 (0)

IMT = Inspiratory Muscle Training group, SEM = standard error of the mean.

[#] p =0.051 between IMT and control groups.

Table 13: Characteristics of participants in Study 4 who died during hospital admission

Age, Gender	Main Diagnosis on ICU admission	APACHE II score (Risk of Death)	Cause of Death (during or after intervention period)	Co-morbidities
74, Male	Perforated duodenal ulcer	24 (0.65)	Major hemorrhage secondary to perforated duodenal ulcer (during)	HTN, GORD, dyslipidemia
78, Female	Coronary artery bypass grafting	39 (0.93)	Septic shock, aortic dissection, acute renal failure (during)	IHD, NIDDM, HTN, hyperlipidemia, hypothyroidism, GORD
61, Male	Coronary artery bypass grafting	24 (0.07)	Multiple organ failure, decompensated chronic liver disease & encephalopathy (after)	Alcoholic liver disease, HTN, GORD, AF
40, Male	Hepatorenal syndrome	25 (0.15)	Pleural effusion, renal failure & fluid overload +/- dilated cardiomyopathy (after)	Alcoholic liver cirrhosis, GORD, hypercholesterolemia, recurrent septicemia, recurrent syncopal episodes

APACHE II = acute physiology and chronic health evaluation score, HTN = hypertension, GORD = gastroesophageal reflux disease, IHD = ischaemic heart disease, NIDDM = non-insulin-dependent diabetes mellitus, AF = atrial fibrillation.

DISCUSSION

We have shown for the first time that in the post-extubation period, participants who complete 2 weeks of IMT have greater improvement in respiratory muscle strength than those who do not train. This is congruent with previous studies of IMT in mechanically ventilated patients(Cader et al., 2010, Martin et al., 2011, Condessa et al., 2013) and with the rapid strength gains within 2 weeks of commencing IMT previously described in healthy cyclists (e.g. increased MIP scores by 8.4%(Johnson et al., 2007)). It is possible that some of the apparent strength gains could be attributable to a learning effect, given the similarity between the IMT technique and the MIP testing manoeuvre. However, in intensive care patients rapid atrophy has been observed in both skeletal(Puthucheary et al., 2013) and respiratory muscles(Levine et al., 2008) within the first few days of admission. With an adequate training stimulus, some of these changes could be reversible within a relatively short timeframe. Regardless of the underlying mechanism of improvement, the apparent strength gains in this cohort translated into benefits in quality of life, which is arguably a more important patient-centred outcome than inspiratory muscle strength.

Our inability to demonstrate an improvement in inspiratory muscle endurance in the IMT group is somewhat surprising, as IMT has been shown to increase proliferation of both Type 1 and Type 2 inspiratory muscle fibres(Ramirez-Sarmiento et al., 2002) and endurance benefits of IMT have been reported after 8 weeks of training in patients with chronic obstructive pulmonary disease(Hill et al., 2006), after 11 weeks of training in athletes(Volianitis et al., 2001) and after 4 weeks of training in recreationally active people (Bailey et al., 2010). While it is possible that the specific training regime employed in our study translates into strength benefits alone, it is more likely that the duration of training was insufficient to effect a measurable improvement in endurance, or that the FRI is insufficiently sensitive to detect subtle changes in endurance over such a short time frame. A more sustained constant loading test may have better elucidated changes in inspiratory muscle endurance, however our experience with these participants resonated with that of Chang and colleagues(Chang et al., 2005a) who found a limited tolerance for even the basic 2 minute FRI test. Thus measuring inspiratory muscle endurance in this patient group remains a challenge.

The statistically significant improvements in quality of life in the IMT group, as measured with the EQ5D tool (Figure 18a), warrant further exploration. The magnitude of change in EQ5D scores (14 in the IMT group compared to 2 in the control) is likely to be clinically important in this group which struggles with poor quality of life following weaning. While the IMT group commenced from a lower baseline EQ5D score (41 in the IMT group compared to 51 in the control) we believe it is unlikely that there was a ceiling effect in this cohort, as scores at 2 weeks remained well below maximal values (i.e. mean 54% across both groups). We would expect quality of life to continue a slow trajectory of improvement beyond the ICU stay(Herridge et al., 2011) but it is possible that IMT provides an advantage early in this trajectory.

Although the IMT group expressed improved quality of life using the EQ5D tool, the effect was less marked when assessed by the SF36. This may reflect difficulty in completing all components of the longer SF36 questionnaire. One of the challenges in ICU outcomes research is the effect of residual cognitive impairment(Iwashyna et al., 2010) and fatigue on a participant's ability to complete lengthy quality of life assessment tools. The reasons for improved quality of life in the absence of a demonstrated effect on respiratory endurance, dyspnoea or functional level, remain unclear.

Improvements in inspiratory muscle strength did not have a clinically or statistically significant impact on the other patient-centred outcomes in this study. While physical function improved similarly in both groups, it is likely that other aspects of treatment (e.g. whole body exercise and gait retraining) had a stronger influence on recovery of physical function than IMT. The fact that both groups improved in terms of physical function may reflect the high standard of usual care in this unit, which includes early rehabilitation and mobilisation. Thus, the findings of this study may only be generalisable to acute settings where early mobilisation and rehabilitation are the norm. Furthermore, the failure of IMT to significantly affect reintubation rates or length of stay may be attributable to the small sample size, as the effect size of IMT may be very small in relation to the many other variables that impact on these clinically significant outcomes. Future studies of IMT in the post-weaning period should be adequately powered to further clarify these relationships.

The difference in in-hospital mortality between groups was unexpected, although the mortality in the IMT group (12%) was close to that anticipated in the trial design (12.8%). To our knowledge, no increase in mortality has been reported with IMT in any population to date, including ventilated intensive care patients, or patients with chronic obstructive pulmonary disease or heart failure. As summarised in Table 13, none of the deaths appeared to be related directly to IMT or respiratory complications. Given the small number of study participants and heterogeneity of diagnoses, further study of the impact of IMT on in-hospital mortality is indicated before robust conclusions about mortality can be drawn.

Limitations of this study include a loss to follow up of 17%, which should have been partly offset by the planned sample size augmentation of 15% to account for anticipated mortality. A lack of follow-up of primary outcomes beyond 2 weeks is another limitation. Moreover, some patients may benefit from ongoing IMT beyond a 2 week training period, particularly as most did not return to 100% of predicted MIP values during this study. In patients with chronic obstructive pulmonary disease, IMT has longer-term benefits including lower rates of hospitalisation over a 12 month period(Beckerman et al., 2005). It is possible therefore that IMT in the post-extubation period has ongoing effects which should be assessed further.

With regard to the training device, a ceiling effect was problematic in 2 participants whose MIP exceeded 82 at baseline. As the maximum resistance setting on the device is 41cmH_2O, it was impossible to provide training at greater than 50% of MIP in these 2 participants. While all other participants commenced at 50% MIP intensity during the training period, 16 participants (47%) achieved the 41cmH_2O maximal setting on the device at some point during the 2 week period, limiting further incremental training. Thus our study may have underestimated the potential impact of IMT. In future studies of IMT we recommend using a device with the capacity to provide higher training intensities, such as an electronic device(Langer et al., 2015). Furthermore, future studies may target those with identifiable strength deficits, as these may constitute a subgroup which is most likely to benefit from training, while those with high baseline values have probably diluted the potential benefits of training in our cohort.

This study is the first to demonstrate the value of IMT for patients in the post-extubation period. IMT can be considered an effective strategy to reverse some of the residual inspiratory muscle weakness which is common following prolonged mechanical ventilation, and may enhance quality of life in these patients with just 2 weeks of training. Future studies of intensive care patients in the post-extubation period should further explore the impact of IMT on quality of life, as well as the longer term effects of IMT in this group, including effects on mortality.

CHAPTER 6: Study 5

Protocol for a Randomised Controlled Trial of Inspiratory Muscle Training to Hasten Recovery from Mechanical Ventilation

This chapter has been published in the peer-reviewed journal BMJ Open and is reproduced with permission (Appendix C):

http://bmjopen.bmj.com/content/2/2/e000813.abstract

Bissett B, Leditschke IA, Paratz J, Boots R (2012). *Protocol: Inspiratory Muscle training for Promoting Recovery and Outcomes in Ventilated patients (IMPROVe): a randomised controlled trial.* BMJ Open **2**;2 (2):e000813.

INTRODUCTION

Mechanical ventilation used in intensive care units, whilst often essential in the management of respiratory failure, can result in respiratory dysfunction and inspiratory muscle weakness (Tobin et al., 2010). Even patients who can successfully wean from mechanical ventilation may suffer impaired fatigue resistance of the inspiratory muscles following successful weaning (Chang et al., 2005a). Inspiratory muscle weakness has been associated with difficulty weaning from mechanical ventilation (De Jonghe et al., 2007) and the degree of weakness is correlated with the duration of ventilation (Chang et al., 2005a, De Jonghe et al., 2007). One case-control study demonstrated that mechanical ventilation results in increased proteolysis and atrophy in the diaphragm muscle, while other skeletal muscles are spared (Levine et al., 2008). Clearly inspiratory muscle weakness is likely to be at least one of the factors that could contribute to difficult and prolonged weaning from mechanical ventilation (Bissett et al., 2012c).

Inspiratory muscle training with a threshold device has been used in patients with chronic lung disease for many years, resulting in not just increased inspiratory muscle strength, but also increased inspiratory muscle endurance, reduced dyspnoea and increased exercise tolerance and quality of life (Shoemaker et al., 2009). Since 2002, case reports of inspiratory muscle training in ventilator-dependent patients have suggested that inspiratory muscle training is associated with favourable weaning outcomes (Sprague and Hopkins, 2003, Martin et al., 2002, Bissett and Leditschke, 2007). More recently, two randomised trials (Cader et al., 2010, Martin et al., 2011) using different training strategies have demonstrated benefits of inspiratory muscle training for ventilated patients, including statistically significant increases in inspiratory muscle strength (Martin et al., 2011, Cader et al., 2010) reduced weaning time by a mean of 1.7 days (Cader et al., 2010) and a higher rate of successful weaning at day 28 (71% compared to 47%)(Martin et al., 2011) . However the generalisability of these results is limited by the sub-groups studied (aged over 70(Cader et al., 2010), failed to wean(Martin et al., 2011)) as well as the sedation and rehabilitation approaches used in the investigating centres units. It is not yet known whether similar results would apply to a more heterogeneous group of intensive care patients in an Australian context. For example an approach of minimal sedation and early active rehabilitation may result in different training effects and relative benefits of inspiratory muscle training. It is also not known which training parameters are optimal.

In an analysis of 195 inspiratory muscle training treatments in ventilated patients, inspiratory muscle training was found to be safe with zero adverse outcomes and stable physiological parameters in response to training (blood pressure, heart rate, oxygen saturation and respiratory rate)(Bissett, 2012). However, the mechanisms of improvement with inspiratory muscle training in ventilated patients have not been investigated. It is theoretically feasible that a high-intensity training protocol could provide an adequate training stimulus to halt or reverse diaphragmatic atrophy and proteolysis (Levine et al., 2008). As has been shown in athletes, inspiratory muscle training could also attenuate a sympathetically-mediated metaboreflex, resulting in enhanced limb muscle perfusion (Witt et al., 2007). This improved limb perfusion could facilitate early mobilisation, resulting in enhanced functional capacity or quality of life.

The following protocol outlines the process by which we intend to answer some of these questions with regards to inspiratory muscle training in a heterogeneous group of patients who have been ventilator-dependent for seven days or longer in our Australian intensive care unit setting. The protocol describes a randomised trial of patients who commence inspiratory muscle training whilst still ventilated.

STUDY OVERVIEW:

This trial (RCT1) examines the effects of inspiratory muscle training on post-weaning outcomes for patients who undergo mechanical ventilation for at least 7 days and commence training while ventilator-dependent. This trial was registered with the Australia New Zealand Clinical Trials Registry December 13 2010 (ACTRN12610001089022).

Aims:

RCT1 aims to answer the following questions:

1. Does inspiratory muscle training, commenced while mechanically ventilated, affect the fatigability of respiratory muscles following weaning from prolonged mechanical ventilation (> 7 days)?
2. Does inspiratory muscle training, commenced while mechanically ventilated, affect the duration of ventilation required or the rate of reintubation in these patients?
3. Is there a measurable difference in the stress response and / or anabolic response in patients undergoing inspiratory muscle training, compared to routine physiotherapy?
4. Does inspiratory muscle training affect dyspnoea, quality of life or functional measures or post-intensive care length of hospital stay following successful ventilatory weaning?

Hypotheses:

The hypotheses are that inspiratory muscle training will reduce inspiratory muscle fatigability, dyspnoea and possibly duration of ventilation and post-intensive care length of hospital stay, and will improve quality of life and functional measures in this population without concomitant increases in the stress response or detectable changes in muscle anabolism.

METHOD:

The randomized controlled trial will be conducted, with the anticipated flow of patients described in Figure 19. Randomisation for the study will be provided through a computer generated random number sequence, managed off-site by clerical staff unconnected with the study, and accessible to the investigators only via telephone to ensure concealed allocation. All intensive care patients will be screened daily for study eligibility by the senior intensive care physiotherapist. Eligible participants will be invited to participate and subsequently enrolled by the chief investigator and baseline measures completed prior to allocation.

A total of 70 participants will be required for RCT1. On the basis of data extrapolated from previous case series this provides a power estimate for expected differences in fatigue resistance indices between the groups of 0.8, if α = 0.05. Sample sizes have been inflated 15% to account for the known mortality of this patient population (12.8%) (Canberra Hospital intensive care unit audit data 2009).

Subjects:

Subjects will be recruited from Canberra Hospital intensive care unit (Canberra, Australia). Patients mechanically ventilated for more than 7 days who are alert and able to co-operate with training (Riker sedation agitation score(Riker et al., 1999) of 4) and can provide informed consent will be randomised (computer generated random number sequence, concealed allocation) to receive either inspiratory muscle training or usual physiotherapy care. Usual physiotherapy care typically involves deep breathing exercises (without a resistance device), manual hyperinflation (Blattner et al., 2008), secretion clearance techniques, assisted mobilisation (Schweickert et al., 2009, Morris et al., 2008) and upper and lower limb exercise as indicated.

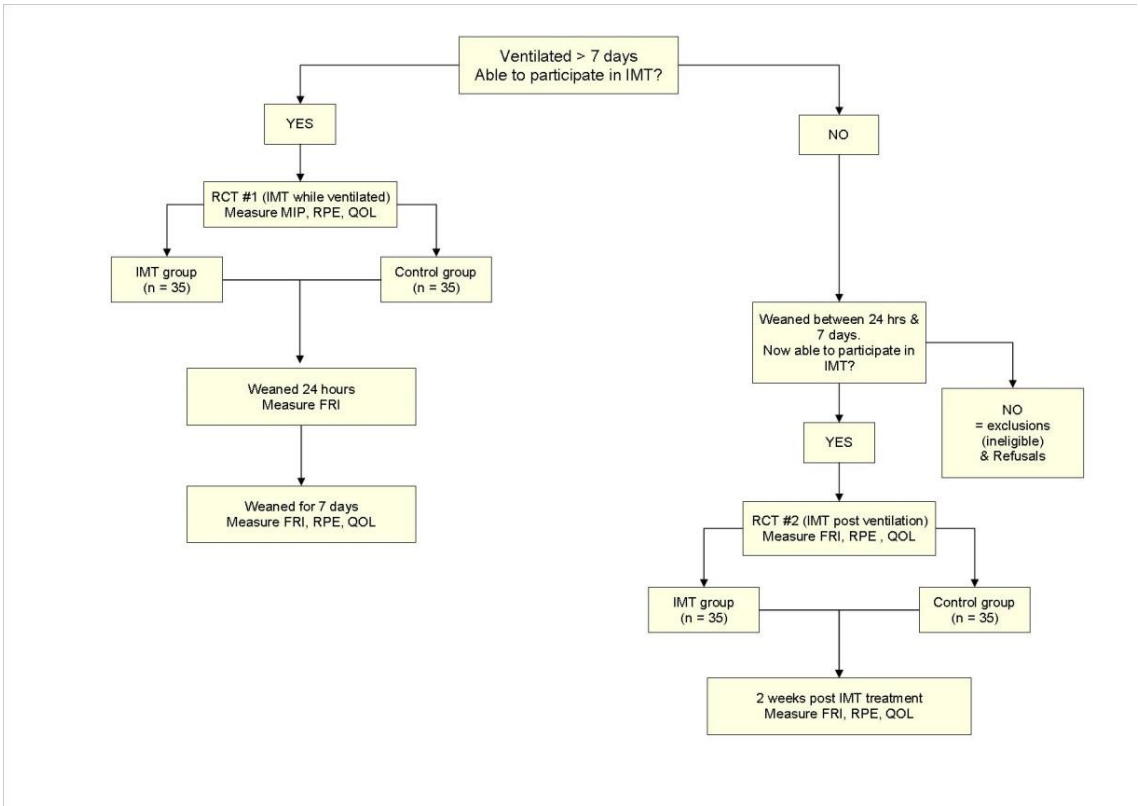

Figure 19: Flow of participants through Study 5.
(N.B. RCT2 refers to the patients already described in Study 4).

Inclusion criteria

All patients admitted to the intensive care unit who:

- are mechanically ventilated through invasive means for 7 days or longer
- are aged ≥ 16 years
- are alert and able to co-operate with training (Riker score 4)
- are able to provide informed consent
- are haemodynamically stable and requiring minimal ventilatory support (i.e. PEEP ≤10)

Exclusion criteria

Patients will be excluded from RCT 1 if they are:

- undergoing non-invasive ventilation only
- aged < 16 years
- unwilling to consent or not able to provide informed consent
- previously included in RCT 1 (i.e. patients readmitted to intensive care)
- pregnant
- mechanically ventilated less than 7 days
- not alert or able to co-operate with training (Riker score < 4 or > 4)
- requiring high levels of ventilatory support (e.g. PEEP > 10 cm H_2O, FiO_2 > 0.60, nitric oxide, nebulised prostacycline, high frequency oscillation) and / or where the treating team (medical and / or physiotherapy) deems risks of brief disconnection from ventilation unacceptable
- medically unstable (e.g. new cardiac arrhythmia, acutely septic) where the treating team (medical and / or physiotherapy) consider interference with ventilatory support could compromise patient's recovery; and / or are deemed suitable for palliation
- experiencing significant pain which interferes with breathing capacity (e.g. fractured ribs): inspiratory muscle training could be reconsidered when pain is controlled and patient is able to participate

Outcome measures: Table 14 summarises the outcome measures used in Study 5.

Table 14: Outcome measures used in Study 5

OUTCOME MEASURE	Timing of Assessment
Fatigue Resistance Index (FRI) (Primary outcome measure)	• 24 hours post weaning • 7 days post weaning
Maximum Inspiratory Pressure (MIP)	• Commencement of training • 24 hours post weaning • 7 days post weaning
Quality of Life / Functional assessments (SF-36, EQ-5D, Acute Care Index of Function)	• Commencement of training • 7 days post weaning
Rate of Perceived Exertion (RPE) at rest and during training	• Commencement of training • 7 days post weaning
Duration of mechanical ventilation (days)	✓
Duration of weaning (from commencement of pressure-support only to 24 hrs ventilator-free)	✓
Post ICU-discharge length of hospital stay (days)	✓
Hospital discharge destination (including in-hospital mortality)	✓
ICU readmission rates	✓
Reintubation rates (%) – defined as reintubation required within 48 hours of extubation	✓
Urinary cortisol, creatinine and urea levels	• Commencement of training • Day 7 of training

Interventions, samples and assays:

Muscle trainer:

Inspiratory muscle training will be performed using the Threshold inspiratory muscle trainer (Threshold IMT device HS730, Respironics NJ, USA). This device has been validated in both healthy patients and those with chronic lung disease (Gosselink et al., 1996) and is superior to alternative flow-resistance devices due to its reliability in ensuring prescribed pressures are achieved regardless of participant's flow rate (Gosselink et al., 1996).

The training parameters are based on previously published case studies (Bissett and Leditschke, 2007, Martin et al., 2002, Sprague and Hopkins, 2003) and are consistent with evidence-based inspiratory muscle training guidelines in patients with chronic lung disease (Hill et al., 2010) which recommend that high intensity interval training is well tolerated and

optimises outcomes (Hill et al., 2006). The physiotherapist prescribes the highest tolerable intensity that allows the participant to just complete the 6th breath in a set of 6 breaths (Martin et al., 2011). The intensity is gradually increased by the physiotherapist across the training period to provide adequate training stimulus. Training is performed daily on week days, with the physiotherapist assisting the patient to perform 5 sets of 6 breaths each session. Between sets, patients are returned to the ventilator for a rest period as required (typically less than 60 seconds). The whole training session takes less than 10 minutes per day.

Training will be provided by either the chief investigator, senior intensive care physiotherapist or a physiotherapy department staff member who has been trained and credentialed in the technique in accordance with our previously published protocol (Bissett and Leditschke, 2007).

Respiratory strength and fatigue measurement

Inspiratory muscle strength will be measured as maximum inspiratory pressure (MIP), in accordance with the protocol described by the American Thoracic Society and European Respiratory Society (Green et al., 2002). Briefly, this technique requires the patient to maximally inhale from residual volume into a hand-held pressure manometer and sustain the effort for more than 1 second. Nose clips are not required. The patient is coached to ensure adequate lip seal around the mouth piece and achieve maximum voluntary effort, and the effort is repeated until at least 3 measurements have less than 20% variability between them (Green et al., 2002).

The device used to perform MIP testing is a portable MicroRPM Respiratory Pressure meter (CareFusion, San Diego, USA) (Australian Therapeutic Goods Administration approval 166760). Such hand-held devices have demonstrated reliability and validity (Hamnegard et al., 1994) and are easy to use at the bedside in intensive care or ward environments. The device will be zeroed and calibrated before each measurement.

The method of determining fatigue resistance capacity is the protocol used by Chang and colleagues (Chang et al., 2005a) and is based on the Maximum Incremental Threshold Loading test described in the American Thoracic Society / European Respiratory Society guidelines (Clanton et al., 2002). Following successful weaning from mechanical ventilation (i.e. within 24 – 48 hours), the patients' fatigue resistance (FRI) is calculated. Following 3 MIP measurements (as above), participants breathe through inspiratory resistance (through the Threshold inspiratory muscle training device) equivalent to 30% of the initial MIP for 2 minutes. This level of resistance has been selected as the preliminary trials by Chang et al indicated that resistance equivalent to 50% of MIP resulted in severe dyspnoea (Chang et al., 2005a). If the participant is not able to inspire at 30% of their MIP, no resistance is applied. MIP measurements are repeated at 2 minutes.

During the loading task, the testing will be ceased if the RPE is ≥ 7, pulse oximetry saturation falls > 10% from initial values or to < 90%, or the heart rate increases by> 30 beats per minute. FRI is calculated comparing the pre- and post-loading values of the MIP (i.e. Post MIP / Pre MIP). The FRI procedure is repeated 7 days post successful weaning from ventilation.

Cortisol & urea sampling

Patients with an indwelling catheter in situ will have 24 hours urine at baseline and Day 7. Urine will be assayed for cortisol, creatinine and urea using High Performance Liquid Chromatography.

Dyspnoea (shortness of breath):

Dyspnoea will be measured using a Modified Borg scale (RPE categorical score out of 10) which has been found to have acceptable reliability and validity in patients undergoing mechanical ventilation (Powers and Bennett, 1999). RPE will be recorded both at rest and during exercise at successful weaning (24 hours) and 1 week post weaning (by a blinded assessor).

Quality of Life and Functional measures:

Quality of Life is measured using the SF-36v2 tool (acute 1 week time frame) and the EQ-5D tool as one combined survey. The SF-36 tool has demonstrated reliability, responsiveness, construct and criterion validity and is responsive to clinical improvement in an intensive care population(Hayes et al., 2000). The EQ-5D tool has also been used in intensive care patient follow-up (Granja et al., 2003) and is likely to give a more global measure of health-related quality of life. The survey will be completed on enrolment and 7 days following successful weaning.

Functional level will be measured using the Acute Care Index of Function (ACIF) which has good levels of inter-rater reliability (Van Dillen and Roach, 1988) and construct validity (Roach and Van Dillen, 1988) in acute neurological conditions.

TERMINATION CRITERIA:

An individual would be withdrawn from the study in the case of death, withdrawal of consent or ability to participate actively. Should a patient in the view of the treating physician not tolerate the intervention, for whatever reason, the patient may be withdrawn from the study, however follow up data including FRI would still be collected and all data collected will be analysed on an intention to treat basis. Adverse outcomes are not anticipated, due to the demonstrated safety of the technique in our own pilot data (Bissett, 2012), and the lack of documented adverse sequelae in other studies (Martin et al., 2002, Sprague and Hopkins, 2003, Martin et al., 2011, Cader et al., 2010).

According to a recent multi-site study on the safety of physiotherapy intervention in intensive care (Zeppos et al., 2007), the following criteria would cause the treating therapist to cease the intervention immediately and alert on-site medical attention (i.e. senior intensive care registrar): alteration in blood pressure > or < 20% resting; alteration in heart rate < or > 20% resting; new arrhythmia; oxygen desaturation > 10%; pulmonary artery pressure (systolic) > 60 mmHg; suspected pneumothorax; agitation risking detachment of equipment or lines or requiring increase sedation. Should such an episode occur, the participant's suitability for remaining in the trial would be reviewed by the Chief Investigator, in consultation with senior intensive care medical staff.

MINIMISING BIAS:

Outcome measures will be taken by blinded assessors, however therapists providing the intervention cannot be blinded.

Patients will be informed that the study is investigating different types of 'breathing exercises', without reference to a device, thus allowing blinding of the patients. Although a sham comparison would be ideal, most sham interventions with the threshold device have used low training pressures (e.g. 9 – 11 cm H_2O). The concern is that for the weakest patients, this level of training can be challenging. In our pilot case series(Bissett, 2012) several participants trained for several sessions with pressures below 15 cm H_2O pressure, generating RPE scores of > 7. Our observations are also substantiated by the work of DeJonghe et al(De Jonghe et al., 2007) who were able to quantify the median MIP for ventilated patients who have returned to consciousness as only 30 cm H_2O. That is, a mere 9 cm H_2O training pressure would equate to 30% of MIP, and 30% intensity has shown training benefits in patients with chronic obstructive pulmonary disease (Preusser et al., 1994, Lisboa et al., 1994, Sanchez Riera et al., 2001). Thus it would be difficult to use a true sham without risking inadvertent 'training' of the weakest patients. As an alternative to a true 'sham' comparison, the control participants will receive daily coached breathing exercises (deep breathing or demand ventilation exercises without a threshold device) to minimise the potential Hawthorne effect.

PROPOSED METHODS OF DATA ANALYSIS:

Data will be analysed using both an intention to treat and per protocol analysis with a carry forward analysis for missing data. Mean changes scores, standard deviations and 95% confidence intervals will be calculated between groups for pre and post intervention. It is anticipated that the analysis will use a combination of t-tests, chi square tests and repeated measures ANOVA (or non-parametric equivalents) as appropriate. If missing data is a problem a mixed model may be used. There will be a baseline comparison of age, gender, APACHE II scores, highest SOFA score, and length of stay. There will be *a priori* stratification of those participants with known neuromuscular disease (e.g. Guillain Barre, Motor Neurone Disease, Myaesthenia Gravis).

Predictive Modeling:

A sub-study of RCT1 will analyse the correlation between inspiratory muscle training pressures (cm H_2O) and duration of weaning (hours off ventilator in a 24 hour period). If possible a mathematical model linking these two variables will be described.

CONTINGENCIES:

Should participant recruitment prove slow to reach the required sample size for this study, the study duration may be increased by 6 to 12 months as required, pending ongoing ethics approval.

DATA MANAGEMENT:

A custom-designed database will store de-identified patient data in a secure password-protected file accessible only to designated research office staff. Data will be entered by blinded research office staff from hard copies which are stored in a locked office. Data completeness will be reviewed by research office staff quarterly and cross-referenced with existing medical records. The investigators will only have access to the database on completion of the study.

CONCOMITANT INTERVENTIONS:

All usual physiotherapy interventions, including early mobilisation as is the standard of care in both ICUs, will be allowed. No specific medical or surgical interventions are disallowed for trial participants other than those described in the exclusion criteria above.

ETHICS AND DISSEMINATION

Ethics approval has been gained for these studies through these institutional committees:

1. Australian Capital Territory Health Human Research Ethics Committee (ETH 10.10.370)
2. University of Queensland Medical Research Ethics Committee (2010001488)

Any adverse events connected with the trial would be immediately reported to these committees as well as registered through the hospital risk management system.

The results of this study will be presented at national and international intensive care and physiotherapy conferences, and will be submitted for publication in peer reviewed journals particularly focused on intensive care medicine.

DISCUSSION

The findings of this study would be highly relevant to intensive care staff who address the challenges of ventilatory weaning and physical rehabilitation. Any intervention which can hasten weaning from mechanical ventilation, or recovery following intensive care stay, is highly likely to reduce overall length of stay and may reduce associated morbidity and mortality. In addition to the individual patient benefits that this will produce, there is the potential for a substantial community economic benefit due to reduced hospital costs.

If efficacy of inspiratory muscle training can be demonstrated, this could lead to a change in intensive care practice internationally across disciplines, including physiotherapy, respiratory therapy, nursing and intensive care medicine. Ultimately, the people most likely to benefit from this study are the patients, with improved understanding of methods to optimise treatment and minimise the complications of prolonged mechanical ventilation.

UPDATE & ETHICAL DISCUSSION OF CONTINUATION OF STUDY 5

Recruitment for Study 5 commenced in February 2011, and following screening of 282 patients, 48 of the required 70 participants have been enrolled in the study (as of December 2015). Based on current recruitment rates the new projected time frame for completion of this study is December 2017. Since February 2011, there have been no adverse events associated with any of the IMT sessions and as expected, based on Study 1, these have been well-tolerated by patients.

In light of the unexpected in-hospital mortality findings in Study 4, we deemed it prudent to conduct an interim analysis of in-hospital mortality in Study 5. As stated in the protocol for Study 5, we anticipated high mortality in this group and inflated sample sizes by 10% to allow for this. Indeed the mortality rate in Study 4 (4 of 70, 5%) was not surprising, although the fact that all 4 deaths were in the IMT group was unexpected. As of November 2015, there does not appear to be an association with in-hospital mortality in Study 5, with small numbers of patients dying in both treatment and control groups prior to hospital discharge.

We have provided feedback to the ACT Health Human Research Ethics Committee about the unexpected mortality finding in Study 4, including the specific causes of death (i.e. Table 13) which appear to be unrelated to respiratory failure. We have also reiterated that Study 4 was underpowered for mortality and the finding is particularly fragile given the very small numbers involved. The fact that 2 of the patients died weeks after cessation of IMT (2 and 5 weeks respectively) makes it difficult to directly link the mortality finding with the intervention. In this context, and in light of the fact that no other study of IMT in ventilator-dependent patients to date has reported increased mortality, we have been encouraged by the committee to continue Study 5 and will continue to monitor in-hospital mortality closely.

It is also hoped that the examination of cortisol levels in Study 5 will further enhance understanding of any stress response associated with IMT. Although the results of Study 1 suggest that high-intensity IMT is well-tolerated physiologically, the cortisol results will further contribute to our understanding of the safety of IMT in ventilator-dependent patients.

Thus as a research team we are confident that we have extensively explored the reasons behind the unexpected mortality finding in Study 4, and are satisfied that it is ethically sound to continue completion of Study 5 as per the advice of the ethics committee. Although the timeframes required for completion of Study 5 prohibit its inclusion in this thesis (due to slow recruitment), this final element of the project will continue to be overseen by this research team to ensure it is completed to the highest possible standard and the results are disseminated widely. Extension of ethical approval through the ACT Health Human Research Ethics Committee has been accordingly obtained until 2017.

CHAPTER 7: DISCUSSION

FINDINGS AND CONCLUSIONS

The major findings of this project are that patients who undergo mechanical ventilation for more than 7 days are likely to develop deficits in inspiratory muscle strength, with approximately one third also developing impaired inspiratory muscle endurance following successful ventilatory weaning. These deficits occur even when patients have been managed with spontaneous modes of ventilation and early proactive mobilisation. Further, this project has demonstrated that inspiratory muscle training is feasible and safe in selected mechanically-ventilated patients who are alert and able to participate with training. However, for those who cannot participate in inspiratory muscle training while ventilated, it would appear that following successful ventilatory weaning, 2 weeks of inspiratory muscle training improves inspiratory muscle strength and quality of life, but does not improve inspiratory muscle endurance.

A secondary finding of this project has been the establishment of the clinimetric properties of the Acute Care Index of Function, an outcome measure that has been used to quantify physical function and activity levels of patients in intensive care. It has excellent inter-rater reliability and reasonable construct validity of the Acute Care Index of Function in intensive care patients, allowing it to be validly used as an outcome measure in the other studies in this project.

Since this project commenced in 2010, there has been an increase in research into inspiratory muscle training in mechanically-ventilated patients. Since 2011, 9 randomised trials of inspiratory muscle training in intensive care patients have been published (Cader et al., 2010, Martin et al., 2011, Condessa et al., 2013, Dixit and Prakash, 2014, Elbouhy et al., 2014, Ibrahiem et al., 2014, Mohamed et al., 2014, Pascotini et al., 2014, Shimizu et al., 2014), and the results of these studies have been summarised in 2 systematic reviews with meta-analyses (Moodie et al., 2011, Elkins and Dentice, 2015). While the meta-analyses confirmed that inspiratory muscle training in ventilator-dependent patients increases respiratory muscle strength and facilitates weaning (Moodie et al., 2011, Elkins and Dentice, 2015), there is wide variability in both patient selection and training programs used across the studies. For example, Cader et al (2010) studied inspiratory muscle training in patients aged over 70 but excluded those with tracheostomies. Given that many

long-term patients in intensive care will require tracheostomy beyond seven days of mechanical ventilation, this exclusion criterion limits the usefulness of the findings of this study. Patients in the study by Martin et al (2011) were a subset of intensive care patients who had failed to wean from mechanical ventilation and underwent training in a specialized weaning unit. These patients had experienced several weeks of mechanical ventilation prior to commencing training, and therefore may be at much higher risk of respiratory muscle weakness than a typical cohort of intensive care patients. In contrast, Condessa et al (2013) did not demonstrate improvements in weaning rates in their intensive care patients, but this may be due to selecting a patient cohort who had only been mechanically ventilated for 48 hours and therefore have less strength deficit initially. Moreover, these researchers only used a training intensity of 40% of maximum inspiratory pressure, which may be an inadequate training stimulus to achieve the strength and weaning benefits demonstrated in other studies. Given the heterogeneity of both patients and training parameters used across the studies to date, further research is needed to identify the intensive care patients who would benefit most from inspiratory muscle training, as well as the ideal training parameters. Study 5, described in Chapter 6, will add to this body of knowledge, particularly as it includes patients of all ages who were ventilated for 7 days or longer, via both endotracheal tubes and tracheostomies. Furthermore it focuses on patient-centred outcomes including physical function and rate of perceived exertion, which other studies in this field have not yet explored.

CONTEXT OF THE FINDINGS

All studies completed in this project were undertaken in an intensive care unit where minimisation of sedation is the standard practice. This may limit the generalisability of the findings of the project, particularly as many intensive care units around the world are still exploring ‘sedation interruption’ as opposed to complete alertness as the standard of care for intubated and ventilated patients. Early mobilisation is also standard practice in this unit, including for ventilated patients (Leditschke et al., 2012). In contrast, other studies of inspiratory muscle training have been performed in units where patients do not actively participate in any other rehabilitation (Condessa et al., 2013), or where the amount of rehabilitation activity was reduced during the training period (e.g. Martin et al (2011) reduced duration and intensity of rehabilitation activities by approximately 50%). It is conceivable that mobilisation and whole body rehabilitation may affect inspiratory muscle strength and endurance, and therefore possible that units which do not practice early rehabilitation may have different outcomes with inspiratory muscle training in their patients

relative to those demonstrated in this project. The relationship between whole-body exercise and specific respiratory muscle function is yet to be studied in the intensive care context, but given the relationships between inspiratory muscle strength and exercise performance in athletes (as described in Chapter 1), the relative effects of global and specific exercise training deserve further exploration in this patient group.

Over the past 5 years there has been a proliferation of research into the effects of early mobilisation and rehabilitation in intensive care (Morris et al., 2011, Team Investigators et al., 2015, Stiller, 2013). While recent suggestions that physiotherapists should focus on early mobilisation as a matter of priority(Stiller, 2013) may have changed the landscape of physiotherapy practice in many units, this suggestion is unlikely to have had a local impact across the life of this project as early mobilisation and rehabilitation were already the norm (Leditschke et al., 2012). Thus despite the relatively long duration of Studies 3, 4 and 5, it would not be expected that the international shift in intensive care physiotherapy paradigm would have compromised the findings of this study. Furthermore, as described in Study 3, early progressive mobilisation and rehabilitation does not safeguard against respiratory muscle impairment and dyspnoea as a consequence of prolonged mechanical ventilation. This information is valuable to clinicians who are focusing on early rehabilitation as dyspnoea may limit exercise tolerance in these patients. Thus the findings of this project are highly relevant to the contemporary intensive care unit which focuses on early proactive rehabilitation.

Despite the recent evidence in favour of inspiratory muscle training in intensive care patients, it is not yet standard practice in most intensive care units around the world. A recent study of French physiotherapists revealed that although many claim to provide inspiratory muscle training to facilitate weaning, only 16% of those surveyed used an evidence-based approach, and only 2% titrated a suitable training intensity from maximal inspiratory pressure (Bonnevie et al., 2015). This study revealed that most physiotherapists considered diaphragmatic breathing control a form of inspiratory muscle training. Based on evidence from many populations (including athletes and those with chronic disease, as outlined in Chapter 1), accurately titrated high resistance is key to obtaining benefits from inspiratory muscle training, whereas there is no evidence to date that deep breathing exercises (without resistance) improve outcomes for ventilator-dependent patients. Thus clinicians should be deterred from confusing deep breathing

exercises with inspiratory muscle training which requires carefully titrated resistance training at precise pressures.

STRENGTHS AND LIMITATIONS OF THE STUDIES

The strengths of the studies contained in this project include the fact that they were performed in a modern tertiary intensive care unit with the usual resources and staffing levels available in Australia. Thus the assessments and treatments studied have occurred in a realistic clinical setting. Furthermore, the robustness of design in Study 4 has minimised bias through randomisation with concealed allocation, blinded outcome assessors for the primary outcomes, dyspnoea and quality of life scores, and intention-to-treat analysis. As with most studies of physiotherapy interventions, it was not possible to blind physiotherapists delivering the interventions in this project. Furthermore, Acute Care Index of Function assessments in these studies were performed by the treating physiotherapist who was not blinded to the intervention. This pragmatic approach may have introduced some bias regarding functional outcomes. Nonetheless, it is a strength of these studies that patient-centred outcome measures were included, as few studies of inspiratory muscle training in intensive care patients have considered the importance of physical function and quality of life.

A limitation of the studies in this project is lack of longer term follow-up beyond hospital discharge. Given the benefits of inspiratory muscle training observed in Study 4 within 2 weeks of training, it would be valuable to know whether these benefits were preserved in the subsequent weeks and months. It would also be worthwhile exploring whether there was any ongoing association between inspiratory muscle strength and quality of life for these patients. Furthermore, it would be informative to examine mortality in the longer term for the participants in Study 4, specifically to ascertain whether the trend in favour of the control group persisted beyond hospital discharge.

The fact that these studies were conducted in a single unit may limit the extrapolation of the findings to intensive care units with very different practices. All patients that participated in Studies 1, 3 and 4 were alert, able to provide consent and participate actively. In intensive care units where patients are mostly sedated, patients will be unable to participate in the inspiratory muscle training described in the protocols for Studies 1, 4 and 5. Even following successful weaning, patients who have experienced prolonged sedation may suffer the residual effects of long-term sedation on cognitive function (i.e.

delirium), and may not be able to participate adequately in inspiratory muscle training. Thus sedation practices must be considered when determining whether the findings of this project could be applied to intensive care units around the world.

Similarly, in units where early mobilisation is not standard practice, it is unknown whether the impact of inspiratory muscle training would be different. Given the wide variety in practices of early mobilisation around Australia (Berney et al., 2013) and the world (Chawla et al., 2014, Malone et al., 2015, Nydahl et al., 2014), it is probably prudent to limit extrapolations of these findings to units with similar practices regarding mobilisation and rehabilitation.

In light of these concerns regarding external validity, these studies should be replicated in other intensive care units around the world to ensure the robustness and generalisability of the findings. Ideally these studies should be powered to detect changes in both quality of life and in-hospital mortality.

CLINICAL IMPLICATIONS

The findings of this project have several implications for clinicians working in intensive care. The results from Study 3 suggest that clinicians can anticipate considerable inspiratory muscle weakness, manifesting as elevated dyspnoea both at rest and during exercise, in patients recently weaned from mechanical ventilation of at least 7 days' duration. This knowledge can be used by medical, nursing and allied health clinicians to reassure patients that their symptoms are normal and, based on Study 4, are likely to improve within 2 weeks. Furthermore, if physiotherapists wish to enhance inspiratory muscle strength and quality of life in these patients, they may use high-intensity inspiratory muscle training and anticipate positive results within 2 weeks in the majority of patients.

This project also provides clinicians with confidence that inspiratory muscle training can be performed safely in selected ventilator-dependent patients. If physiotherapists use the high intensity interval-approach described in Study 1, the patient is likely to maintain adequate oxygenation without supplemental oxygen, and they are likely to remain cardiovascularly stable. However the efficacy of this training approach for ventilator-dependent patients is yet to be demonstrated, and the results of Study 5 will be highly relevant to clinicians with regards to prioritising this intervention.

Based on the findings of Study 2, intensive care physiotherapists may confidently utilise the Acute Care Index of Function to quantify the functional trajectory of intensive care patients. Most importantly, clinicians can identify patients with a score of less than 0.40 at intensive care discharge, and proactively direct rehabilitation resources towards these patients, or use this information to guide discharge planning. This information will be of great clinical relevance not just to physiotherapists, but also the whole multidisciplinary team who continue to care for the patient following discharge from intensive care.

FURTHER RESEARCH

While this project has demonstrated the value of inspiratory muscle training in the post-weaning period, it would be worthwhile determining whether such benefits also occur when inspiratory muscle training is commenced while patients are mechanically-ventilated. While Study 1 established the safety of high-intensity interval training for selected ventilator-dependent patients, the protocol outlined in Chapter 6 (Study 5) is a robust exploration of the efficacy of inspiratory muscle training in this group, including important patient-centred outcomes like physical function, dyspnoea and quality of life. The consistency of measures between Studies 4 and 5 will also allow valuable comparisons to be made in future.

This project has highlighted numerous challenges with studying long-term intensive care patients, including the intermittent delirium and impaired cognition which can make completion of lengthy outcome measures problematic in this patient group. Future studies may benefit from selecting outcome measures which do not require sustained attention spans (i.e. selecting EQ5D in preference to SF36). Furthermore, these studies have highlighted the limitations of simple spring-loaded inspiratory muscle trainers, which can thwart training efforts through a ceiling effect at an intensity of 41 cm H_2O. Since this study was designed, there has been much progress in the development of electronic inspiratory muscle training devices (Langer et al., 2015) which have a much wider training bandwidth and may therefore be better suited to training intensive care patients. The feasibility and utility of these devices deserves exploration in both ventilator-dependent and spontaneously breathing intensive care patients.

As one of the findings of Study 4 was that quality of life appears to improve with just 2 weeks of inspiratory muscle training, this is worth exploring in a larger multi-centre study which is powered to detect improvements in quality of life. Such a study should ideally evaluate the effects of inspiratory muscle training beyond the initial 2 week training period.

Given that many of the patients in Study 4 had not yet returned to 100% of their predicted values of maximum inspiratory pressure by 2 weeks, there is potential benefit from continuing training for several more weeks and evaluating the impact on quality of life and dyspnoea symptoms over several months.

Finally, the trend towards higher mortality in the treatment group in Study 4 should be further investigated with a longer term follow-up of this patient cohort to determine whether mortality remains elevated between the groups in the longer term. It will be valuable to collect follow-up data from this cohort specifically comparing morbidity and mortality between 1 and 5 years of intensive care survival.

CLOSURE

The findings of this project have been disseminated widely, including presentation at the European Society of Intensive Care Medicine (2011), the Australian Physiotherapy Association Conference (2011), International Physical Medicine and Rehabilitation Conference (2013), Australia New Zealand Intensive Care Society Scientific Meeting (2013, 2015) and the Canberra Health Annual Research Meeting (2011, 2014, 2015). An abstract for Study 4 has also been submitted to the American Thoracic Society conference for 2016.

As reproduced with permission in Appendices B to F, the literature review and studies have been published in both Australian and international peer-reviewed journals. Copies of these articles have been provided to funding bodies and ethics review committees for their records. Furthermore, the results have been presented to stakeholders including staff in the intensive care unit and physiotherapy department at Canberra Hospital, as well as the University of Queensland.

All data has been de-identified and stored electronically in the Canberra Hospital Intensive Care Research office in accordance with ethical requirements. The ACT Health Human Ethics Review Committee has been advised of the in-hospital mortality results described in Study 4.

Recruitment for Study 5 has commenced and at time of thesis submission, is at 48 of 70 patients (since February 2011). This study has extension of ethics approval to continue until recruitment has been finalised (anticipated 2017).

SUMMARY

The combined findings of this project have implications for the current practice of physiotherapy and intensive care medicine. First, clinicians can recognise inspiratory muscle weakness and fatigability as a likely consequence of prolonged mechanical ventilation. These residual impairments are likely to manifest as dyspnoea both at rest and during exercise for many patients in the post-weaning period. Second, inspiratory muscle weakness can be at least partly reversed with high-intensity inspiratory muscle training in the post-weaning period, with just two weeks of daily training resulting in improvements in both inspiratory muscle strength and quality of life. Third, inspiratory muscle training is safe in selected ventilator-dependent patients and supplemental oxygen is not required to maintain respiratory and cardiovascular stability during and after training. Fourth, the Acute Care Index of Function is reliable and valid in intensive care patients, and can be used to predict hospital discharge destination. This new information provides the ability to target rehabilitation and direct resources to patients who require it most. These combined findings are a patient-centred and clinically-meaningful contribution to the existing body of knowledge regarding rehabilitation of intensive care patients.

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APPENDIX A:

The effects of inspiratory muscle training in other populations

Given the efficacy of inspiratory muscle training in both athletes and patients with chronic obstructive pulmonary disease, is it not surprising that inspiratory muscle training has increasingly been explored in other patient populations. Although neither the quality nor quantity of the evidence in other groups is comparable to that previously described, it is worth comparing the application of inspiratory muscle training in different states of pathology as this give further insight into possible causative mechanisms and ideal training parameters. Furthermore, patients admitted to intensive care often have several comorbidities (e.g. chronic heart failure or kidney failure), which makes discussion of inspiratory muscle training in these groups all the more pertinent.

Chronic heart failure

Early published case studies of inspiratory muscle training in chronic heart failure (Mancini et al., 1995, Cahalin et al., 1997) were compromised by low adherence to training protocols (e.g. 63%), low training intensity (e.g. 20% MIP) and lack of a control group. An early randomised trial of inspiratory muscle training in chronic heart failure was also confounded by a potentially ineffective sham comparison, where 15% of MIP may have provided a training effect in the control group (Johnson et al., 1998), while another early randomised trial was also limited by high drop-out rates and ineffective blinding (Weiner et al., 1999). In the context of these shortcomings, improvements in MIP of up to 32% were reported (Cahalin et al., 1997) with most of this change detectable in the first 2 weeks of training, which is similar to findings in healthy people described previously.

Two subsequent randomised trials (Dall'Ago et al., 2006, Padula et al., 2009) both employed a relatively low training intensity (30% MIP) for 12 weeks training 20 - 30 minutes per day. While both studies found significant improvements for chronic heart failure patients in terms of MIP (e.g. 115%)(Dall'Ago et al., 2006) and dyspnoea, the study of the home-based nurse-supervised program (Padula et al., 2009) failed to detect significant changes in quality of life as measured by the SF-36 tool. In contrast, the inspiratory muscle training program supervised once-weekly by a physiotherapist (Dall'Ago et al., 2006) demonstrated not just improvements in exercise performance and quality of life (as measured by the Minnesota Living with Heart Failure Questionnaire), but also

improved circulatory power and oxygen uptake kinetics. Importantly, this study also showed that the improvements in MIP and quality of life were sustained up to 12 months following cessation of training. A contemporaneous study (Laoutaris et al., 2007) further showed that high intensity training (60% MIP) resulted in superior benefits compared to low intensity training (15% MIP) in terms of exercise tolerance and dyspnoea measures. Moreover, this latter study also showed that inspiratory muscle training was not associated with significant anti-inflammatory effects in patients with chronic heart failure.

Studies which selectively studied chronic heart failure patients with inspiratory muscle weakness found significant effects for inspiratory muscle training in terms of oxygen uptake or adaptions of blood flow distribution. Using a relatively low training stimulus (30% MIP) and an endurance-type protocol (30 minutes per day for 12 weeks), Winkelmann and colleagues (2009) failed to show significant results for exercise tolerance and quality of life in patients with chronic heart failure, but did detect significant improvements in VO_{2max} and MIP in the training group. For patients with known inspiratory muscle weakness, inspiratory muscle training has also been shown to increase blood flow to limbs during exercise (Chiappa et al., 2008) as well as improve oxygen uptake efficiency (Stein et al., 2009) when patients trained at 30% of maximal intensity for 30 minutes daily for 12 weeks. These results provide some clues as to how inspiratory muscle training may enhance exercise capacity in chronic heart failure and are not dissimilar to findings in athletic populations. These findings also reinforce the importance of identifying patients with inspiratory muscle weakness and targeting them selectively with inspiratory muscle training.

Chronic kidney disease

The benefits of inspiratory muscle training have been explored to a limited extent in patients with chronic kidney disease. In a randomised trial of patients undergoing haemodialysis (Pellizzaro et al., 2013), patients who underwent inspiratory muscle training 3 times per week for 10 weeks at an intensity of 50% of maximum inspiratory pressures demonstrated greater gains in inspiratory muscle strength than those who completed only peripheral exercise or no exercise while on dialysis. Greater gains were also seen with the inspiratory muscle training group compared with the control group in distance walked during the 6 minute walk test (65 m versus -0.5 m respectively). This study also demonstrated benefits of inspiratory muscle training with regards to sleep, which was significantly greater in the inspiratory muscle training group than both the peripheral

training and control groups. While no other studies of inspiratory muscle training have explored sleep benefits specifically, these findings deserve further exploration in other populations where poor sleep impacts on quality of life.

It is not yet known whether inspiratory muscle training may benefit patients with chronic kidney failure in the pre-dialytic phase of the disease. However given the known detrimental impact of chronic kidney disease on health-related quality of life (Unruh and Hess, 2007), it would be worth exploring whether the benefits seen in the dialytic population also extend to those managing the disease in the earlier phases.

Cystic Fibrosis

There are only a few articles published which investigate the effects of inspiratory muscle training in cystic fibrosis. One study of inspiratory muscle training in children with cystic fibrosis (Sawyer and Clanton, 1993) found that 10 weeks of daily training at 60% of MIP for 30 minutes resulted in increased inspiratory muscle strength (13%), increased exercise capacity (10%) and subjectively enhanced sputum clearance. This is one of very few studies in the inspiratory muscle training literature to describe an increase in lung volumes (i.e. vital capacity 14%, total lung capacity 11.6%) as a result of inspiratory muscle training. The authors speculated that this change in lung volume may be in part due to the young age of the participants involved, who may still be benefiting from alveolar multiplication.

A more recent randomised study of inspiratory muscle training in adults with cystic fibrosis (Enright et al., 2004) found further evidence that inspiratory muscle training increases both lung volumes and diaphragm thickness, but also improves psychosocial status and exercise capacity. However these benefits were found at a training intensity of 80% of MIP, and not at 20% of MIP. This also compares with a previous non-randomised trial of 16 patients with cystic fibrosis (de Jong et al., 2001) which found that 6 weeks of training at an intensity of 40% of MIP resulted in increased inspiratory muscle strength, but not measures of exercise capacity, lung volumes, dyspnoea or fatigue. Overall, these results echo the findings in the wider literature that intensity of inspiratory muscle training is critical.

In 2008 a Cochrane systematic review (Houston et al., 2008) of inspiratory muscle training in cystic fibrosis found the overall quantity and quality of research in this field so limited that meta-analysis was not possible, and suggested that clinicians consider using

inspiratory muscle training on a case by case basis. Given the slow emergence of convincing evidence for the efficacy of inspiratory muscle training in patients with chronic lung disease over the past few decades, where early studies were similarly confounded by variable training equipment and low intensities, it is arguably premature to dismiss the potential of inspiratory muscle training to improve quality of life, lung function and exercise tolerance in both children and adults with cystic fibrosis. Specific quantitative analysis of the impact of inspiratory muscle training on sputum clearance would be useful in this particular patient group.

Asthma in children

Whilst most trials of inspiratory muscle training have used training frequencies of between 3 and 7 days per week, one study of inspiratory muscle training in asthmatic children aged between 8 and 12 (Lima et al., 2008) was unusual in that training was performed just twice a week for 7 weeks. Particularly in paediatric patients, minimising treatment sessions may enhance training compliance. Although this study showed improvements in MIP, maximum expiratory pressure and peak expiratory flow (a key indicator of disease severity in asthma), the interpretation of the results are limited by the fact that inspiratory muscle training was delivered in combination with deep breathing exercises, purse-lipped breathing and fractionated breathing, while control participants experienced education only; thus it is impossible to isolate the true effect of inspiratory muscle training alone in this study. Nonetheless, given the positive results reported, the question of optimal training frequency with inspiratory muscle training remains unanswered in this patient group.

Pre-operative surgical patients

As patients undergoing thoracic or abdominal surgery are at risk of postoperative pulmonary complications (Haines et al., 2013, Scholes et al., 2009, Reeve et al., 2010, Wynne and Botti, 2004), the idea that inspiratory muscle training may provide a degree of prophylaxis against postoperative pulmonary complications is attractive. For patients undergoing cardiac surgery, 2 weeks of daily pre-operative inspiratory muscle training reduced post-operative decline in lung function and gas exchange compared to a control group (Weiner et al., 1998). In this study significantly more patients in the control group required longer than 24 hours of mechanical ventilation, and whether this is attributable to the effects of inspiratory muscle training, or is rather a confounding variable, remains to be determined.

A more recent investigation of patients undergoing cardiac surgery(Hulzebos et al., 2006), which selectively included those at high risk of post-operative pulmonary complications, found that 2 to 4 weeks of preoperative inspiratory muscle training resulted in significantly lower post-operative pulmonary complications in the inspiratory muscle training group (18%) compared to the control group (35%). These authors also reported a trend towards shorter length of stay but this failed to reach statistical significance despite the large sample size (n = 279).

There is limited evidence to support the use of pre-operative inspiratory muscle training to prevent postoperative pulmonary complications in abdominal surgery, with a one pilot study (Dronkers et al., 2008) showing trends towards increased inspiratory muscle strength and less atelectasis in the inspiratory muscle training group. However the small sample size (n = 20) and lack of statistical significance (p = 0.07) means these results must be interpreted with caution. A second pilot study (Kulkarni et al., 2010) compared 2 weeks of pre-operative inspiratory muscle training, deep breathing exercises, incentive spirometry and no therapy. Whilst this study observed a significant post-operative preservation of MIP in the inspiratory muscle training group only, it was also confounded by a small sample size (20 per group) and a high drop-out rate (> 25%) with a lack of intention-to-treat analysis. This study also reported surprisingly low levels of postoperative pulmonary complications, perhaps because it deliberately excluded those with known or suspected respiratory infections. As acknowledged by the authors, it may be useful to selectively study those at high risk of developing postoperative pulmonary complications in determining the true clinical usefulness of preoperative inspiratory muscle training in abdominal surgery patients.

While research into the effects of inspiratory muscle training as a pre-operative intervention is in its infancy, it would not be surprising if surgeons welcome the potential of pre-operative inspiratory muscle training as a standard measure in the near future, considering the low financial burden and potential benefit in terms of post-operative outcomes.

Spinal cord injury

Since the mid-1990s several studies have specifically describe the effects of inspiratory muscle training in patients with spinal cord injury. The first (Rutchik et al., 1998), a case series of 10 patients with chronic spinal cord injury (level C4 – C7 for longer than 1 year),

observed that inspiratory muscle training for 15 minutes twice daily for 8 weeks resulted in improvements in lung volumes (i.e. forced vital capacity, vital capacity, total lung capacity and functional residual capacity). However a reduction in dyspnoea in the experimental group did not reach statistical significance, possibly due to the small sample size. Furthermore, changes in lung volumes and dyspnoea were not maintained 6 months following cessation of inspiratory muscle training.

The second observational study (Wang et al., 2002) focused on sleep-disordered breathing in 14 patients with traumatic spinal cord injury. While these researchers detected a small increase in MIP and a small reduction in carbon dioxide levels during sleep following 6 weeks of inspiratory muscle training, this study was confounded by limited monitoring of the treatment intervention, where patients saw the therapist only every second week, and furthermore no attempt was made to increase the training intensity over time. Thus the adherence to the training protocol and the training stimulus itself may be questioned. Furthermore, the conclusions that can be drawn from this and the previous observational study are limited due to the absence of a control group.

A third study (Liaw et al., 2000) randomly allocated 20 patients with acute spinal cord injury (level C4 -C7 for less than 6 months) to either inspiratory muscle training or control groups, where inspiratory muscle training was performed for 15 minutes twice daily for 6 weeks. These authors found greater improvements in lung volumes in the inspiratory muscle training group (i.e. total lung capacity, vital capacity, forced expiratory volume in 1 second) but also found significant improvements in dyspnoea in the inspiratory muscle training group compared to control. However, the absence of an intention-to-treat analysis, in the context of several drop-outs, may be of concern in interpreting these results.

Whilst promising, these initial results must be interpreted with caution as all studies employed a resistance device where intensity was flow-dependent and adequate training stimulus cannot be guaranteed. More recently an observational study of 8 patients with spinal cord injury at levels C4-C7 (Silveira et al., 2010) used a threshold device to provide inspiratory muscle training at 30% of MIP for 30 minutes on weekdays for 8 weeks. While improvements in MIP and forced vital capacity were observed at the end of the program, the lack of a control group was a major limitation. Further randomised studies of inspiratory muscle training in spinal cord injury using threshold-based devices would be useful in

determining whether high intensity inspiratory muscle training produces similar, or potentially greater, benefits in this population.

Amyotrophic Lateral Sclerosis

A randomised trial of inspiratory muscle training in 19 patients with amyotrophic lateral sclerosis (Cheah et al., 2009) failed to find significant results in terms of changes in lung volumes or inspiratory muscle strength. It is possible that the early training parameters used (weeks 1 to 4) were of inadequate intensity (15 – 60% of sniff nasal inspiratory pressure) to induce change, particularly in the context of the wider literature where high intensity training has been vital. It is also possible that the lack of significant results was due to the small sample size.

Moreover there were significant issues with the sham training used: by removing the spring-loaded valves from the inspiratory muscle training devices to produce sham devices for the control group, there was an audible difference in the training between those with intact devices and those using a sham. This lack of audible noise invalidated the blinding of the assessors and possibly of the patients as well. Furthermore, the fact that the control group also increased their lung volumes significantly suggests that in this patient group, the sham device provided some degree of training effect, masking the overall effect of inspiratory muscle training. When studying patients with low baseline level of inspiratory muscle strength, such as those with amyotrophic lateral sclerosis, motor neurone disease or long term ventilator-dependent patients, the potential training effects of the sham device must be carefully considered.

Parkinson's disease

One study has investigated the effect of inspiratory muscle training in patients with Parkinson's Disease (Inzelberg et al., 2005). Despite a small sample size (n = 20), this randomised trial found that 30 minutes of inspiratory muscle training performed 6 days per week for 12 weeks resulted in significant improvements in inspiratory muscle strength and perception of dyspnoea in the inspiratory muscle training group. Of interest, the training parameters were very similar to those described above in the study of patients with amyotrophic lateral sclerosis and similarly found no significant change in lung volumes following inspiratory muscle training. The failure of to detect changes in health-related quality of life in this study raises interesting questions regarding the importance of

dyspnoea for functional performance in this patient group and these deserve further exploration.

Myaesthenia Gravis

The benefits of inspiratory muscle training have also been studied in patients with myasthenia gravis, with one randomised trial (Fregonezi et al., 2005) demonstrating that a combined program of inspiratory muscle training and purse-lipped breathing resulted in significant improvements in inspiratory muscle strength, endurance and chest wall mobility. While this study failed to detect changes in lung function (as measured by spirometry), it unusually detected an improvement in maximum expiratory pressures as a result of inspiratory muscle training. Given the well-accepted specificity of inspiratory muscle training, the authors speculated that this surprising result may be due to enhanced chest wall mobility in this particular patient group. These results must be interpreted with caution, due to the combination of therapies applied.

Muscular Dystrophy

There is limited evidence regarding the effect of inspiratory muscle training in patients with Muscular Dystrophy. One randomised trial (Wanke et al., 1994) used specially-designed equipment to provide inspiratory muscle training through a resistive circuit whilst still ensuring adequate flow. This small study showed improvements in MIP only in those patients whose baseline vital capacity exceeded 25% of predicted values. Interestingly, when improvements did occur, these were still detectable up to 6 months following completion of the inspiratory muscle training program. These authors concluded that inspiratory muscle training may be beneficial in the early stages of muscular dystrophy. A subsequent long-term observational study of patients with either muscular dystrophy or spinal muscular atrophy (Koessler et al., 2001) found that patients could train up to 2 years with daily inspiratory muscle training, resulting in increased MIP, however the improvements appeared to plateau at 10 months. Nonetheless, a plateau may be preferable to respiratory deterioration in this particular patient group.

Poliomyelitis

A non-randomised study of 10 patients with prior poliomyelitis and part-time ventilator-dependence (Klefbeck et al., 2000) observed increased endurance capacity from 10.7 to 16.7 cm H_2O following 10 weeks of daily inspiratory muscle training. However the clinical significance of this change could be questioned and furthermore only 7 of 10 patients

completed the training, thus further research would be required to describe the effect of inspiratory muscle training on this patient group.

Multiple Sclerosis

There is some evidence that a 10 week regime of daily inspiratory muscle training improves inspiratory muscle weakness (MIP) as well as lung function (FEV1, FVC) in patients with multiple sclerosis (MS)(Fry et al., 2007). However this trial only included patients with mild to moderate physical disability. Another randomised trial of inspiratory muscle training in patients with severe MS (Klefbeck and Hamrah Nedjad, 2003) (i.e. 70% wheelchair bound and 30% bedridden) also demonstrated increased MIP following a 10 week inspiratory muscle training program, but failed to demonstrate any spirometric changes. This may be due to the reduced training frequency (every other day) or rather a reflection of the severity of the underlying pathology. Future studies of inspiratory muscle training in patients with MS should consider patient-centred variables such as quality of life to determine the clinical usefulness of inspiratory muscle training in this population.

Healthy elderly

One small pilot double-blind randomised trial of inspiratory muscle training in healthy elderly patients (Aznar-Lain et al., 2007) found that 8 weeks of inspiratory muscle training 5 times per week, with 8 – 10 sets of 5 breaths at 50 – 80% of MIP, resulted in increased MIP, enhanced exercise tolerance and increased physical activity in the inspiratory muscle training group. This study also demonstrated increased VO_{2max} in the experimental group, a finding less commonly reported in studies of younger healthy or athletic patients. However, interpretation of this study's findings is compromised by its small sample size, as well as the fact that the control group had a significantly higher body mass index and were less physically active at baseline than the treatment group.

Other conditions

Inspiratory muscle training has also been reportedly used to treat inspiratory muscle weakness in a wide variety of pathological conditions including laryngeal papilloma (Sapienza et al., 1999), idiopathic diaphragm paralysis (Chatham et al., 2009, Petrovic et al., 2009), bilateral abductor vocal fold paralysis (Baker et al., 2003), and exercise-induced inspiratory stridor (Dickinson et al., 2007). Most authors describe a high-intensity regime resulting in increases in inspiratory muscle strength, reductions in dyspnoea and one group of researcher described successful weaning from nocturnal non-invasive ventilation

(Petrovic et al., 2009). While this latter result was described in the context of an absence of change in phrenic nerve latency, suggesting that spontaneous recovery was not a factor, all these results must be interpreted with caution as they are case reports only and further clinical trials are required to ascertain the true efficacy of inspiratory muscle training in the presence of these conditions.

Summary of inspiratory muscle training in other populations

There is very strong evidence that inspiratory muscle training improves inspiratory muscle strength in athletes and patients with chronic obstructive pulmonary disease, and some evidence that similar results can also be obtained in patients with chronic heart failure, cystic fibrosis, degenerative neurological conditions and spinal cord injury. Whilst there is strong evidence that inspiratory muscle training also improves exercise performance in athletes and patients with chronic obstructive pulmonary disease, this is yet to be clearly demonstrated in other patient groups. Regardless of patient presentation or sporting arena, it would appear that intensity and modality of training are critical to the success of any inspiratory muscle training regime. Also, the perception of dyspnoea may be affected by inspiratory muscle training and the link between inspiratory muscle weakness, dyspnoea and functional performance deserves further consideration. There is much potential to further investigate the potential benefits of inspiratory muscle training across a wide spectra of pathological conditions, with particular focus on patient-centred outcomes including exercise tolerance and quality of life.

APPENDIX B:

Ethical Approvals & Institutional Insurance Agreement

ACT Health Human Research Ethics Committee
Level 6 Building 10, The ACT Health Research Office, Canberra Hospital ACT 2605
PO Box 11 Woden ACT 2606
Phone: 02 6205 0846 Fax: 02 62443092
Website: www.health.act.gov.au
ABN: 82 049 056 234

Dr Anne Leditschke
ICU Research
Building 12 Level 3
Canberra Hospital
Garran ACT 2605

Dear Dr Leditschke

Re: ETHLR.10.408

The ACT Health Human Research Ethics Committee's Low Risk Sub-Committee received notification of the proposed study:

Inspiratory muscle training is safe in selected ventilated patients: a case series at its meeting of 15 December 2010.

I am pleased to inform you that your application has been approved.

The Sub-Committee agreed that the application is for low risk research and determined that the research meets the requirements of the National Statement on Ethical Conduct in Human Research and is ethically acceptable.

I attach for your records an Outcome of Consideration of Protocol form.

I confirm that the ACT Health Human Research Ethics Committee is constituted according to the National Health and Medical Research Council Guidelines and operates in compliance with applicable regulatory requirements and the International Conference on Harmonization Guidelines on Good Clinical Practice.

Yours sincerely

Professor John SG Biggs MA MD
FRCOG FRANZCOG DHMSA
Chairman
ACT Health Human Research Ethics Committee

17 December 2010

ACT HEALTH HUMAN RESEARCH ETHICS COMMITTEE

Outcome of Consideration of Protocol

Submission No: **ETHLR.14.213** **Date of Approval:** **1 September 2014**

Project Title: Reliability and validity of the ACIF tool in Critical Care Patients

Submitted by: Ms Bernie Bissett

Your project was considered by the ACT Health Human Research Ethics Committee and Approved for a period of 3 years.

First Annual Review due: September 2015

The Ethics Committee require as part of the review process that:

- At regular periods, and not less frequently than annually, Principal Investigators are to provide reports on matters including:
  - security of records
  - compliance with approved consent procedures and documentation
  - compliance with other approved procedures.
  - as a condition of approval of the protocol, that Investigators report immediately:
  - adverse affects on subjects
  - proposed changes in the protocol
  - unforeseen events that might affect continued ethical acceptability of the project.
- All published reports to carry an acknowledgement stating:
  - Approved on 1 September 2014 by the ACT Health Human Research Ethics Committee's Low Risk Sub-Committee.

Louise Morauta

Louise Morauta PSM PhD
Chair
ACT Health Human Research Ethics Committee
Low Risk Sub Committee

1 September 2014

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Reliability and Validity of the ACIF Tool in Critical Care Patients
Chief Investigator:	Ms Bernie Bissett
Supervisor:	Dr Jennifer Paratz
Co-Investigator(s):	None
School(s):	UQ School of Medicine; Canberra Hospital
Approval Number:	2014001220
Granting Agency/Degree:	PhD
Duration:	30th September 2015

Comments/Conditions:

Expedited review on the basis of approval from ACT Health HREC dated 01/09/2014

Note: If this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Signature _____ Date 12 Sept 2014

ACT Health Human Research Ethics Committee
Building 10, Level 6, ACT Health Research Office, Canberra Hospital ACT 2605
PO Box 11 Woden ACT 2606
Phone: 02 6205 0846 Fax: 02 62443092
Website: www.health.act.gov.au
ABN: 82 049 056 234

Ms Burnie Bissett
Physiotherapy Department
Building 3 Level 1
Canberra Hospital
Garran ACT 2605

Dear Ms Bissett,

Re: ETH.10.10.370

The ACT Health Human Research Ethics Committee considered the proposed:

Inspiratory Muscle Training for Ventilated patients (> 7 days) at its meeting of 8 November 2010.

I am pleased to advise you that the study has been approved including:

- ACT Health Application form
- Sample size calculations table
- Inspiratory muscle training protocol (ventilated patients)
- Patient Information Sheet, version received October 2010
- Consent form, version received October 2010
- Salary budget costings
- Quality of Life Survey (SF36v2 and EQ-5D)

I confirm that the ACT Health Human Research Ethics Committee is constituted according to the National Health and Medical Research Council Guidelines and operates in compliance with applicable regulatory requirements and the International Conference on Harmonization Guidelines on Good Clinical Practice.

I attach for your records an Outcome of Consideration of Protocol form.

A copy of your application will be sent to ACT Insurance Authority for consideration. Please note that this may take up to four weeks for more complex matters.

The study cannot commence until you receive written approval from the Insurance and Legal Liaison Manager, Mr Simon Fenton, who can be contacted on (02) 620 50928. Any enquiries regarding insurance matters must be addressed to Mr Fenton.

Yours sincerely

John Biggs

Professor John SG Biggs MA MD
FRCOG FRANZCOG DHMSA
Chairman
ACT Health Human Research Ethics Committee

10 November 2010

ACT HEALTH HUMAN RESEARCH ETHICS COMMITTEE

Outcome of Consideration of Protocol

Submission No: ETH.10.10.370 Date of Approval: 10 November 2010

Project Title: Inspiratory Muscle Training for Ventilated patients (> 7 days).

Submitted by: Ms Burnie Bissett

Your project was considered by the ACT Health Human Research Ethics Committee and Approved for a period of 3 years.

Review due: November 2011

The Ethics Committee require as part of the review process that:

- At regular periods, and not less frequently than annually, Principal Investigators are to provide reports on matters including:
  - security of records
  - compliance with approved consent procedures and documentation
  - compliance with other approved procedures.
  - as a condition of approval of the protocol, that Investigators report immediately:
  - adverse affects on subjects
  - proposed changes in the protocol
  - unforeseen events that might affect continued ethical acceptability of the project.
- All published reports to carry an acknowledgement stating:
  - approved on 10 November 2010 by the ACT Health Human Research Ethics Committee.

John Biggs

PROFESSOR JOHN SG BIGGS, CHAIR 10 November 2010

THE UNIVERSITY OF QUEENSLAND

Institutional Approval Form For Experiments On Humans Including Behavioural Research

Chief Investigator:	Ms Bernie Bissett
Project Title:	The Effect Of Inspiratory Muscle Training On The Residual Respiratory Muscle Weakness And The Quality Of Life Of Ventilated Patients
Supervisor:	Dr Jenny Paratz, Dr Robert Boots, Dr Anne Leditschke
Co-Investigator(s):	Margot Green, Dr Anne Leditschke, Dr Jenny Paratz, Dr Robert Boots
Department(s):	School of Medicine, UQ; Physiotherapy Dept & Intensive Care Unit, Canberra Hospital
Project Number:	2010001488
Granting Agency/Degree:	PhD
Duration:	31st December 2013

Comments:

Expedited review on the basis of approval from the ACT Health HREC, dated 10/11/2010.

Name of responsible Committee:-
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:-
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Date: 24.11.2010 Signature:

ETH.10.10.370 - Insurance confirmed

2 messages

Fenton, Simon <Simon.Fenton@act.gov.au> 15 December 2010 at 15:16
To: "berniembissett@gmail.com" <berniembissett@gmail.com>, "Bissett, Bernie" <Bernie.Bissett@act.gov.au>
Cc: ACTHealth-HREC <ACTHealthHREC@act.gov.au>

Hi Bernie,

The ACT Health Human Research Ethics Committee (ACTHHREC) have forwarded your documents to me in order to arrange for the vetting of the insurance and indemnity arrangements for the following study granted ACTHHREC approval recently -

The Effect of Inspiratory Muscle Training on the Residual Respiratory Muscle Weakness and the Quality of Life of Ventilated Patients (ACTHHREC Ref. ETH.10.10.370)

Insurance Confirmed

ACTIA and I have reviewed the internal study and are satisfied that it meets ACT Government's Insurance and indemnity requirements and it has accordingly been included within our policy coverage limited to the acts, errors and omissions of the Territory, subject to the ordinary terms and conditions of the policy

Please note, ACT Health's insurance policies cover the respective interests of the Territory only therefore we can only provide coverage for insurance and workers compensation to ACT Government employees involved in this study only. Our assumption is that the other external parties involved will hold their own coverage for insurance and workers compensation for their conduct in this study.

This cover is provided on the basis that:

* ACTHHREC approval has been confirmed;
* Coverage is continuous for the duration of the approval provided by the ACTHHREC; and
* All researchers involved in the conduct of this study outside of ACT Government, provide their own insurance.

Augie - Please file accordingly. I will note that coverage is confirmed on the spreadsheet.

Cheers

Simon Fenton
Manager
Insurance and Legal Liaison Unit
ACT Health
Phone - (02) 620 50928
Fax - (02) 620 50842
Email - simon.fenton@act.gov.au

APPENDIX C: Licences and Permissions:

- Permission / Entitlements to include published articles in thesis:

a) Anaesthesia and Intensive Care

b) Intensive and Critical Care Nursing (Elsevier)

c) Heart and Lung

d) BMJ Open

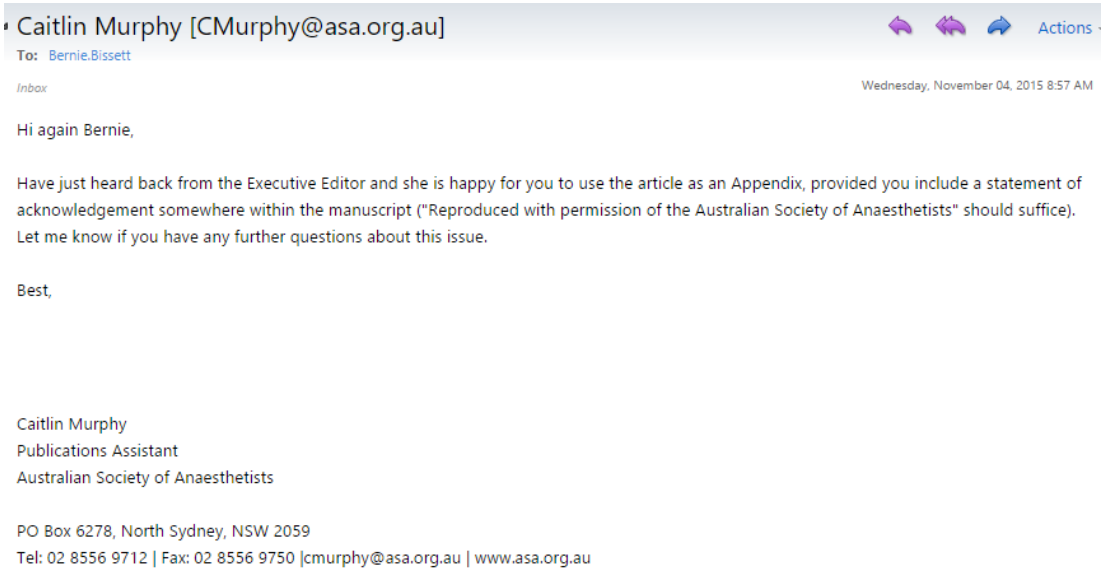
e) Patient consent form (BMJ) relating to Figure 15

- Licences:

a) SF36 Quality of Life Survey Instrument

b) EQ5D Quality of Life Survey Instrument

ANAESTHESIA AND INTENSIVE CARE:



Caitlin Murphy [CMurphy@asa.org.au]

Actions

To: Bernie.Bissett

Inbox

Wednesday, November 04, 2015 8:57 AM

Hi again Bernie,

Have just heard back from the Executive Editor and she is happy for you to use the article as an Appendix, provided you include a statement of acknowledgement somewhere within the manuscript ("Reproduced with permission of the Australian Society of Anaesthetists" should suffice). Let me know if you have any further questions about this issue.

Best,

Caitlin Murphy
Publications Assistant
Australian Society of Anaesthetists

PO Box 6278, North Sydney, NSW 2059
Tel: 02 8556 9712 | Fax: 02 8556 9750 |cmurphy@asa.org.au | www.asa.org.au

INTENSIVE & CRITICAL CARE NURSING:

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If you need any additional assistance, please let us know.

Best Wishes,
Laura

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HEART AND LUNG:

Permission to include article in Thesis

Ardis O'Meara [heartlungjournal@gmail.com]

To: Bernie.Bissett

Cc: Redeker, Nancy [nancy.redeker@yale.edu]

Inbox

Dear Bernie,

Thank you for your message.

Please refer to our website at http://www.heartandlung.org/content/permission for permission to reuse.

Please let me know if you have further questions.

Thank you,
Ardis

Permission Guidelines

For further guidelines about obtaining permission, please review our Frequently Asked Questions below:

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I can confirm that you can include this provided that there's a proper citation/acknowledgement.

Should you have more concern, please let me know.

Kind regards,

Bernadette

Jo Bernadette Berido
Editorial Production Assistant
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PATIENT CONSENT FORM (Figure 15):

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Consent form

For a patient's consent to publication of information about them in BMJ Publishing Group Ltd ("BMJ Group") publications and products.

Name of person described in article or shown in photograph: JULIE GENGE

Subject matter of photograph or article: INSPIRATORY MUSCLE TRAINING

Journal name: THORAX

Manuscript number 208279

Title of article: INSPIRATORY MUSCLE TRAINING TO ENHANCE RECOVERY FROM MECHANICAL VENTILATION: A RANDOMISED TRIAL

Corresponding author: BERNIE BISSETT

I JULIE GENGE [insert full name] give my consent for this information about MYSELF/MY CHILD OR WARD/MY RELATIVE [circle correct description] relating to the subject matter above ("the Information") to appear in the journal and associated publications.*

I have seen and read the material to be submitted to the journal

I understand the following:

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(2) The text of the article will be edited for style, grammar, consistency, and length

(3) The Information may be published in the journal, which is distributed worldwide. The journal goes mainly to doctors but is seen by many non-doctors, including journalists.

(4) The Information will also be placed on the journal website, http://group.bmj.com/products

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(7) I can revoke my consent at any time before publication, but once the Information has been committed to publication ("gone to press") it will not be possible to revoke the consent.

Signed: Julie Genge Date: 5-1-16

BMJ Publishing Group Limited

SF36 LICENCE AGREEMENT (and extension)

QUALITYMETRIC LICENSE AGREEMENT

License Number: QM006395

Effective Date: January 10, 2011

Licensee Name: **ACT Health**

Licensee Address: Level 3, ACT Health Bldg., Canberra City, 2601 Australia

Approved Purpose: Inspiratory muscle training for ventilated patients

Study Name: The Effect of Inspiratory Muscle Training on the Residual Respiratory Muscle Weakness and the Quality of Life of Ventilated Patients

Study Type: Observational

Therapeutic Area: Wellness & Lifestyle

Other Definitions: As indicated on Appendix B "License Agreement – Details", including without limitation: Licensed Surveys, Modes, Fees, Administrations, Services, Approved Languages and (if applicable) License Term

This License Agreement (the "Agreement") is entered into as of the Effective Date, by and between QualityMetric Incorporated ("QM"), 24 Albion Road, Building 400, Lincoln, RI 02865 and Licensee.

Subject to the terms of this Agreement, including the QualityMetric License Terms and Conditions attached as Appendix A: (a) QM grants to Licensee, and Licensee accepts, a non-exclusive, non-transferable, non-assignable, non-sublicensable worldwide license to use, solely for the Approved Purpose and during the License Term, the Licensed Surveys in the authorized Modes and Approved Languages indicated on Appendix B and to administer the Licensed Surveys only up to the total number of Administrations (and to make up to such number of exact reproductions of the Licensed Surveys necessary to support such administrations) in any combination of the specific Licensed Surveys and Approved Languages and Modes and to use any related software provided by QM, (b) Licensee agrees to purchase the Services, and (c) Licensee agrees to pay the Fees in accordance with the invoice to be provided upon execution hereof by Licensee.

Capitalized terms used in this Agreement and not otherwise defined herein shall have the meanings assigned to them in Appendix A. The appendices attached hereto are incorporated into and made a part of this Agreement for all purposes.

EXECUTED, as of the Effective Date, by the duly authorized representatives as set forth below.

QualityMetric Incorporated [Licensor]	**ACT Health** [Licensee]
Signature:_____	Signature: BBissett
Name:_____	Name: BERNIE BISSETT
Title:_____	Title: MRS
Date:_____	Date: JANUARY 11, 2011

APPENDIX B

QualityMetric Incorporated

LICENSE AGREEMENT - DETAILS

Licensee: ACT Health
Bernie Bissett
Yamba Drive
Garran, 2605

License Number: QM006395
Amendment to: N/A
License Term: 11/01/10 to 11/01/13
Master License Term: N/A

Approved Purpose
Inspiratory muscle training forventilated patients

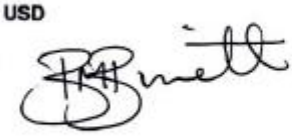
Study Name: Inspiratory muscle training
Protocol:
Govt. ID:
Study Type: Observational
Clients Reference:

Licensed Surveys (Modes) and Services:

Item	Description	Mode of Admin	Quantity
ES0230	SF-36v2, Acute Recall, Project Registration Fee	Paper	1
LANGUAGES	Language Fee		3
ADM012	Patients Enrolled		140
ADMINS	Administrations		280
SS040	Scoring Software v4		1
SS047	Score 8 Domains and 2 Summary Measures		280
SS997	Missing Item Recovery		280
SS996	Data Quality Evaluation DQE/MDE Report		280
SS998	Scoring Software Add-on: UI		280
EM034	Guide to Development of Cert. Modes of Short Form Survey Adm		1
EM035	Guide to Integration of Cert. SF Scoring & DQE Capabilities		1
Approved Languages: United States (English)			
EM036	Guide to Development of Cert. of SF Survey Interp. & Rptng		1
Approved Languages: United States (English)			
NORM055	SF-36v2 General Population Norms 1998		1

TOTAL FEES: **2,882.00 USD**

Payment Terms: **Due on Receipt**



OPTUMInsight

AMENDMENT TO LICENSE AGREEMENT

Effective Date: September 25, 2013

Amendment Number: QM021120
Amendment To: QM006395

Licensee Name: ACT Health
Licensee Address: Yamba Drive
Garran,
2605

Approved Purpose: Inspiratory muscle training forventilated patients

Therapeutic Area: Wellness & Lifestyle

This Amendment to License Agreement (the "Amendment") is entered into as of the Amendment Date, by and between OptumInsight Life Sciences, Inc. (f/k/a QualityMetric Incorporated) ("OptumInsight"), and Licensee.

The following term(s) of the License are modified as indicated below:

License fee:	$475.00
Total Administrations:	280 total administrations
Term:	December 31, 2013 through December 31, 2015
Licensed Surveys:	SF-36v2 Health Survey
Other Change:	Renewal of License through 2015

Except as expressly modified by this amendment, all terms and conditions of the License shall continue in full force and effect without change.

EXECUTED, as of the Effective Date, by the duly authorized representatives as set forth below.

[OptumInsight]		[Licensee]	
OptumInsight Life Sciences, Inc.		**ACT Health**	
Signature:	Michelle White	Signature:	BB Bissett
Name:	Michelle White	Name:	BERNIE BISSETT
Title:	Director of Consulting Science	Title:	SENIOR PHYSIOTHERAPIST
Date:	3 OCT 2013	Date:	3/10/13

EQ5D LICENCE & REGISTRATION:

-------- Original Message --------
Subject:EQ-5D
Date:Fri, 1 Oct 2010 12:15:58 +0000
From:Nalinie Banarsi <banarsi@euroqol.org>
To:berniembissett@gmail.com <berniembissett@gmail.com>

Dear Ms/Mr. Bissett,

Thank you for registering your research at the EuroQol Group's website.

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Kind regards,

Nalinie Banarsi

Office Assistant

EuroQol Group Foundation