Protocol: inspiratory muscle training for promoting recovery and outcomes in ventilated patients (IMPROVe): a randomised controlled trial

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ABSTRACT

Introduction: Inspiratory muscle weakness is a known consequence of mechanical ventilation and a potential contributor to difficulty in weaning from ventilatory support. Inspiratory muscle training (IMT) reduces the weaning period and increases the likelihood of successful weaning in some patients. However, it is not known how this training affects the residual inspiratory muscle fatigability following successful weaning nor patients’ quality of life or functional outcomes.

Methods and analysis: This dual centre study includes two concurrent randomised controlled trials of IMT in adult patients who are either currently ventilator-dependent (>7 days) (n=70) or have been recently weaned from mechanical ventilation (>7 days) in the past week (n=70). Subjects will be stable, alert and able to actively participate and provide consent. There will be concealed allocation to either treatment (IMT) or usual physiotherapy (including deep breathing exercises without a resistance device). Primary outcomes are inspiratory muscle fatigue resistance and maximum inspiratory pressures. Secondary outcomes are quality of life (Short Form-36v2, EQ-5D), functional status (Acute Care Index of Function), rate of perceived exertion (Borg Scale), intensive care length of stay (days), post intensive care length of stay (days), rate of reintubation (%) and duration of ventilation (days).

Ethics and dissemination: Ethics approval has been obtained from relevant institutions, and results will be published with a view to influencing physiotherapy practice in the management of long-term ventilator-dependent patients to accelerate weaning and optimise rehabilitation outcomes.

Trial registration number: ACTRN12610001089022.

ARTICLE SUMMARY

Article focus
- Mechanical ventilation (MV) is known to cause inspiratory muscle weakness, which may contribute to both difficulty weaning and poor recovery.
- Can IMT hasten weaning and enhance recovery from MV if commenced while still ventilated?
- Can IMT enhance recovery if commenced following weaning from MV?

Key messages
- This protocol outlines two concurrent randomised controlled trials that investigate the effects of IMT as a component of early rehabilitation in an Australian intensive care unit.
- The study is designed to capture both physiological measures as well as patient-centred measures of function and quality of life.

Strengths and limitations of this study
- This study is the first of its kind to focus on patient-centred measures and longer term outcomes beyond the period of ventilatory weaning.
- The results of this study will not be generalisable to some intensive care units, which generally keep patients sedated, as patient alertness is a requirement of IMT.

BACKGROUND

Mechanical ventilation (MV) used in intensive care units (ICUs), while often essential in the management of respiratory failure, can result in respiratory dysfunction and inspiratory muscle weakness.1 Even patients who can successfully wean from MV may suffer impaired fatigue resistance of the inspiratory muscles following successful weaning.2 Inspiratory muscle weakness has been associated with difficulty weaning from MV,3 and the degree of weakness is correlated with the duration of ventilation.2,3 One case—control study demonstrated that MV results in increased proteolysis and atrophy in the diaphragm muscle, while other skeletal muscles are spared.4 Clearly, inspiratory muscle weakness is likely to be at least one of the factors that could contribute to difficult and prolonged weaning from MV.5

Inspiratory muscle training (IMT) 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. Since 2002, case reports of IMT in ventilator-dependent patients have suggested that IMT is associated with favourable weaning outcomes. More recently, two randomised trials using different training strategies have demonstrated benefits of IMT for ventilated patients, including statistically significant increases in inspiratory muscle strength, reduced weaning time by a mean of 1.7 days and a higher rate of successful weaning at day 28 (71% compared to 47%). However, the generalisability of these results is limited by the subgroups studied (aged older than 70 years, failed to wean) as well as the sedation and rehabilitation approaches used in the investigating centres. It is not yet known whether similar results would apply to a more heterogeneous group of ICU patients in an Australian ICU context. For example, an approach of minimal sedation and early active rehabilitation may result in different training effects and relative benefits of IMT. It is also not known which training parameters are optimal.

In an analysis of 195 IMT treatments in ventilated patients, IMT 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). However, the mechanisms of improvement with IMT 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. As has been shown in athletes, IMT could also attenuate a sympathetically mediated metaboreflex, resulting in enhanced limb muscle perfusion. 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 regard to IMT in a heterogeneous group of patients who have been ventilator-dependent for 7 days or longer in our Australian ICU setting. The protocol describes two separate but concurrent studies:

1. A randomised trial of patients who commence IMT while still ventilated (randomised controlled trial 1 (RCT1)).

2. A randomised trial of patients who could not participate actively while ventilated but commence IMT within 1 week of successfully weaning from MV (randomised controlled trial 2 (RCT2)).

For clarity in this protocol, ‘the study’ refers to both RCT1 and RCT2 combined. Where RCT1 and RCT2 differ, this will be described explicitly.

**RCT1: OVERVIEW**

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

**Aims**

RCT1 aims to answer the following questions:

1. Does IMT, commenced while mechanically ventilated, affect the fatigability of respiratory muscles following weaning from prolonged MV (>7 days)?

2. Does IMT, 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 IMT compared to routine physiotherapy?

4. Does IMT affect dyspnoea, quality of life or functional measures or post-ICU length of hospital stay following successful ventilatory weaning?

**Hypotheses**

The hypotheses are that IMT will reduce inspiratory muscle fatigability, dyspnoea and possibly duration of ventilation and post-ICU 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.

**Methods**

Two RCTs will be conducted concurrently at two sites, with the anticipated flow of patients described in figure 1. Randomisation for the study will be provided through a computer-generated random number sequence, managed off-site by clerical staff not connected with the study and accessible to the investigators only via telephone to ensure concealed allocation. All ICU patients will be screened daily for study eligibility by the senior ICU 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 subjects 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 (FRI) between the groups of 0.8, if \( \alpha = 0.05 \). Sample sizes have been inflated 15% to account for the known mortality of this patient population (12.8%) (Canberra Hospital ICU Audit data 2009).

**Subjects**

Subjects will be recruited from both Canberra Hospital ICU and Calvary Hospital ICU (both located in Canberra, Australia). Patients mechanically ventilated for more than 7 days who are alert and able to co-operate with training (Riker Sedation—Agitation Score of 4) and can provide informed consent will be randomised (computer-generated random number sequence, concealed allocation) to receive either IMT or usual physiotherapy care. Usual physiotherapy care typically involves deep breathing exercises (without a resistance
device), manual hyperinflation,15 secretion clearance techniques, assisted mobilisation16 17 and upper and lower limb exercise as indicated.

**Inclusion criteria**
All patients admitted to ICU 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 of 4);
- are able to provide informed consent;
- are haemodynamically stable and requiring minimal ventilatory support (ie, positive end expiratory pressure (PEEP) ≤10).

**Exclusion criteria**
Patients will be excluded from RCT1 if they are:

- undergoing non-invasive ventilation only;
- aged <16 years;
- unwilling to consent or not able to provide informed consent;
- previously included in RCT1 (ie, patients readmitted to ICU);
- pregnant;
- mechanically ventilated <7 days;
- not alert or able to co-operate with training (Riker score of <4 or >4);
- requiring high levels of ventilatory support (eg, PEEP >10 cmH2O, FiO2 >0.60, nitric oxide, nebulised prostacyclin, high frequency oscillation) and/or where the treating team (medical and/or physiotherapy) deems risks of brief disconnection from ventilation unacceptable;
- medically unstable (eg, new cardiac arrhythmia, acutely septic) where the treating team (medical and/or physiotherapy) considers that interference with ventilatory support could compromise patient’s recovery and/or are deemed suitable for palliation;
- experiencing significant pain that interferes with breathing capacity (eg, fractured ribs): IMT could be reconsidered when pain is controlled and patient is able to participate.

**Outcome measures**
Table 1 provides a summary of the outcome measures used in RCT1.

**Interventions, samples and assays**
**Muscle trainer**
IMT will be performed using the Threshold IMT inspiratory muscle trainer (Threshold IMT device HS730; Respironics, Parsippany, New Jersey, USA). This device has been validated in both healthy patients and those with chronic lung disease18 and is superior to alternative flow resistance devices due to its reliability in ensuring prescribed pressures are achieved regardless of subject’s flow rate.18

The training parameters are based on previously published case studies7–9 and are consistent with evidence-based IMT training guidelines in patients with chronic lung disease,19 which recommend that high-intensity interval training is well tolerated and optimises outcomes.20 The physiotherapist prescribes the highest tolerable intensity that allows the subject to just complete the sixth breath in a set of six breaths.11 The intensity is gradually increased by the physiotherapist across the training period to provide adequate training stimulus. Training is performed daily on weekdays, with the physiotherapist assisting the patient to perform five sets of six breaths each session. Between sets, patients are
returned to the ventilator for a rest period as required (typically <60 s). The whole training session takes <10 min per day. Training will be provided by the chief investigator, senior ICU physiotherapist or a physiotherapy department staff member who has been trained and credentialled in the technique in accordance with our previously published protocol.9

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.21 Briefly, this technique requires the patient to maximally inhale from residual volume into a handheld pressure manometer and sustain the effort for more than 1 s. Noseclips 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 three measurements have <20% variability between them.21

The device used to perform MIP testing is a portable MicroRPM Respiratory Pressure meter (CareFusion, San Diego, CA, USA) (Australian Therapeutic Goods Administration approval 166760). Such handheld devices have demonstrated reliability and validity22 and are easy to use at the bedside in ICU 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 colleagues2 and is based on the maximum incremental threshold loading test described in the American Thoracic Society/European Respiratory Society guidelines.23 Following successful weaning from MV (ie, within 24–48 h), the patients’ FRI is calculated. Following three MIP measurements (as above), subjects breathe through inspiratory resistance (through the Threshold IMT device) equivalent to 30% of the initial MIP for 2 min. This level of resistance that has been selected as the preliminary trials by Chang and colleagues2 indicated that resistance equivalent to 50% of MIP resulted in severe dyspnoea. If the subject is not able to inspire at 30% of their MIP, no resistance is applied. MIP measurements are repeated at 2 min. During the loading task, the testing will be ceased if the rate of perceived exertion (RPE) is ≥7, pulse oximetric saturation falls >10% from initial values or to <90% or the heart rate increases by >30 beats per minute. FRI is calculated comparing the preloading and postloading values of the MIP (ie, post-MIP/pre-MIP). The FRI procedure is repeated 7 days after successful weaning from ventilation.

Cortisol and urea sampling
Patients with an indwelling catheter in situ will have 24 h 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 MV.24 RPE will be recorded both at rest and during exercise at successful weaning (24 h) and 1 week postweaning (by a blinded assessor).

### Table 1 Outcome measures used in the study

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>RCT1</th>
<th>RCT2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue resistance index (primary outcome measure)</td>
<td>24 h postweaning; 7 days postweaning</td>
<td>Commencement of training; day 14 of training</td>
</tr>
<tr>
<td>Maximum inspiratory pressure</td>
<td>Commencement of training; 24 h postweaning</td>
<td>Commencement of training; day 14 of training</td>
</tr>
<tr>
<td>Quality of life/functional assessments (Short Form-36, EQ-5D, Acute Care Index of Function)</td>
<td>Commencement of training; 7 days postweaning</td>
<td>Commencement of training; day 14 of training</td>
</tr>
<tr>
<td>Rate of perceived exertion at rest and during training</td>
<td></td>
<td>Commencement of training; day 14 of training</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days) and duration of weaning (from commencement of pressure-support only to 24 h ventilator-free)</td>
<td></td>
<td></td>
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<tr>
<td>ICU length of stay (days)</td>
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<td>NA</td>
</tr>
<tr>
<td>Post-ICU discharge length of hospital stay (days) and hospital discharge destination (including in-hospital mortality)</td>
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<td></td>
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<tr>
<td>ICU readmission rates and reintubation rates (%)—defined as reintubation required within 48 h of extubation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary cortisol, creatinine and urea levels</td>
<td>Commencement of training; day 7 of training</td>
<td>NA</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; NA, not applicable; RCT, randomised controlled trial.

Quality of life and functional measures

Quality of life is measured using the Short Form-36v2 tool (acute 1 week time frame) and the EQ-5D tool as one combined survey. The Short Form-36 tool has demonstrated reliability, responsiveness, construct and criterion validity and is responsive to clinical improvement in an ICU population. The EQ-5D tool has also been used in intensive care patient follow-up 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 and construct validity in acute neurological conditions, however, has not been examined specifically in the ICU population. There are unpublished reports of the ACIF being used to measure functional recovery in ventilated patients and other non-neurological acute conditions. In the absence of a more specific tool that has been validated for ICU patients, the construct validity of the ACIF renders it the most useful tool to measure functional recovery in this study.

**RCT2: OVERVIEW**

This trial (RCT2) examines the effects of IMT on outcomes for patients who, for whatever reason, were unable to participate in IMT while still ventilator-dependent but have since weaned from ventilation within the previous 7 days and are now able to participate in training (eg, due to resolution of acute delirium, return of cardiovascular stability, etc). The outcomes of this trial will be analysed in relation to the findings of Chang and colleagues that prolonged MV results in increased fatigability of inspiratory muscles following successful weaning from MV. Given that postweaning outcomes are often poor for patients undergoing prolonged MV, evaluation of IMT as a method to ameliorate residual weakness, and thus accelerate rehabilitation, appears warranted. This trial was registered with the Australia New Zealand Clinical Trials Registry on 13 December 2010 (ACTRN12610001089022).

**Aims**

RCT2 aims to answer the following questions:

1. Does postweaning IMT affect residual inspiratory muscle strength or fatigability in patients ventilated for 7 days or longer?
2. Does postweaning IMT affect dyspnoea levels, quality of life or functional recovery in patients ventilated for 7 days or longer?
3. Does postweaning IMT result in lower rates of reintubation, readmission to ICU or duration of post-ICU hospital stay, in patients who have been ventilated for 7 days or longer?

**Hypotheses**

The hypotheses are that postweaning IMT will improve inspiratory muscle strength, reduce inspiratory muscle fatigability and dyspnoea and improve quality of life and functional measures in this population. Furthermore, it is hypothesised that IMT will result in a lower rate of reintubation and shorter post-ICU length of hospital stay in these patients.

**Methods**

RCT2 is a RCT with concealed allocation, blinded outcome assessors and intention-to-treat analysis. Refer to the second arm of figure 1 regarding anticipated flow of patients through RCT2.

**Subjects**

Subjects will be recruited from both Canberra Hospital and Calvary Hospital ICUs (both in Canberra, Australia). Patients who have recently weaned from MV in ICU (within previous 7 days, where the duration of ventilation was 7 or more days) will be recruited to RCT2, with automatic exclusion of patients included in RCT1. Suitable patients will be randomised (computer-generated randomisation sequence) to receive either IMT (in addition to usual physiotherapy care) or usual physiotherapy care only for 2 weeks postweaning. Usual physiotherapy care typically includes deep breathing exercises (without a resistance device), assisted mobilisation, secretion clearance techniques and upper and lower limb exercises as indicated. Treatment will occur in both ICU and ward environments.

A total of 70 subjects will be required for RCT2. On the basis of data extrapolated from previous case series, this provides a power estimate for expected differences in FRI between the groups of 0.8, if $\alpha=0.05$. Again, sample sizes have been inflated 15% to account for the known mortality of this population (12.8%) (Canberra Hospital ICU Audit data 2009).

**Inclusion criteria**

All patients recently mechanically ventilated who:

- were ventilated for 7 days or longer and weaned from MV in the previous 7 days;
- are aged ≥16 years;
- are alert and able to co-operate with training (Riker score of 4);
- are able to provide informed consent.

**Exclusion criteria**

Patients will be excluded from RCT2 if they are:

- aged<16 years;
- unwilling or unable to provide informed consent;
- previously included in RCT1;
- pregnant;
- mechanically ventilated <7 days;
- not alert or able to co-operate with training (Riker score of <4 or >4);
- experiencing significant pain that interferes with breathing capacity (eg, fractured ribs): IMT could be reconsidered when pain is controlled and patient is able to participate;
- medically unstable or deemed suitable for palliation.

Protocol: inspiratory muscle training for ventilated patients (RCT)

Outcome measures
Table 1 provides a summary of the outcome measures used in RCT2.

Interventions, samples and assays
Refer to RCT1 for details of the Threshold IMT device and training parameters. The only difference for RCT2 is that there will be no return to MV between sets, rather the patient is rested (either on room air or oxygen) as appropriate. As per the previous description, the training session will be directly supervised by the physiotherapist and should take <10 min/day. Training will occur on weekdays from enrolment until 2 weeks later. All other outcome measures will be conducted as previously described in the time frames outlined in Table 1.

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 and the lack of documented complications as only 30 cmH2O. That is, a mere 9 cmH2O training pressure would equal to 30% of MIP, and 30% intensity has shown training benefits in patients with chronic obstructive pulmonary disease (COPD). 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 subjects 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, SDs and 95% CIs will be calculated between groups for preintervention and postintervention. It is anticipated that the analysis will use a combination of t tests, $\chi^2$ tests and repeated measures analysis of variance (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, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, highest Sequential Organ Failure Assessment (SOFA) score and length of stay. There will be a priori stratification of those subjects with known neuromuscular disease (eg, Guillain–Barre, motor neuron disease, myasthenia gravis).

Predictive modelling
A substudy of RCT1 will analyse the correlation between IMT pressures (cmH2O) and duration of weaning (hours off ventilator in a 24 h period). If possible a mathematical model linking these two variables will be described.

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

Data management
A custom-designed database will store deidentified 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 three institutional committees:
1. Australian Capital Territory Health Human Research Ethics Committee (ETH 10.10.370).
2. Calvary Hospital Human Research Ethics Committee.
3. University of Queensland Medical Research Ethics Committee (2010001488).

Any adverse events connected with the trial would be immediately reported to all three committees above 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 that can hasten weaning from MV, or recovery following ICU 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 a potential for a substantial community economic benefit due to reduced hospital costs.

If efficacy of IMT 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 MV.

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Competing interests
None.

Patient consent
Obtained.

Ethics approval
Ethics approval was provided by Australian Capital Territory Health Human Research Ethics Committee and Calvary Hospital Human Research Ethics Committee and University of Queensland Medical Human Research Committee.

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Data sharing statement
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