Early effects of inspiratory muscle training in critical patients submitted to mechanical ventilation: A study protocol for a randomised controlled trial

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Study Protocol

Abstract

Background: Respiratory muscle weakness is one of the primary factors associated with difficulty of ventilatory weaning in critically ill patients. In this sense, inspiratory muscle training (IMT) is a possible facilitator of successful weaning. One of the devices used for IMT is the POWERbreathe®, because it provides a linear pressure load, with the possibility of gradual increments. The effectiveness of early IMT in this population is not yet well known. The aim of this study is to assess the effects of early IMT with a mechanical loading device on the weaning time of patients on invasive mechanical ventilation (primary outcome), respiratory muscle strength, length of stay in the intensive care unit and in the success rate of weaning (secondary outcomes).

Methods: This randomised controlled trial, a single blind evaluation, will be conducted in the intensive care unit of a university hospital on 42 adults, who will be randomly and blindly categorised into the control group, comprising patients who undergo routine physical therapy only, and the training group, comprising patients who undergo routine physical therapy associated with IMT twice a day, with load adjusted daily at 50% of maximum inspiratory pressure, three series of 10 repetitions with one minute rest in between. Both groups will be assessed when patients are eligible for the study and before the ventilatory support withdrawal. Effects of the training will be analysed from the collected data using intention-to-treat analysis. Between-group differences will be measured using generalised estimating equations for data analysis.

Discussion: Results of this trial will likely provide valuable new information on the effects of IMT on weaning time, respiratory muscle strength, length of stay in the intensive care unit and the success rate of weaning in critically ill patients.

Registration: ClinicalTrials.gov, NCT03758573. 29th November 2018.

Background

Mechanical ventilation (MV) is a therapeutic resource frequently used to ensure adequate lung function during general anaesthesia as well as in sick patients in the intensive care unit (ICU) [1,2]. In Brazil, a multi-centre study conducted in four ICUs showed that 41.5% of hospitalised patients require ventilatory support and 9.9% require prolonged MV [3].

Despite its benefits, its prolonged use is associated with an increased risk of infection and a series of complications, including ventilator-induced lung injury and impaired respiratory muscles [3,4,5]. Under MV, the respiratory musculature is relaxed; thus, ICU patients may develop diaphragmatic weakness, characterised by reduced capacity to generate pressure and thickness and thickening fraction of the diaphragm [1,6]. This condition is caused by atrophy and reduced contractility of the muscle fibres [7,8].

In critical patients, increased elastic and resistive forces of the respiratory system generate high loads, causing an imbalance between ventilatory demand and respiratory muscle capacity; therefore, this

situation plays an important role in the occurrence of a weaning failure [9]. In addition, respiratory muscle weakness has been impaired, which increases the risk of ICU and hospital readmission, increased mortality and difficult weaning from MV [10]. Dres *et al.* [11] investigated the prevalence of muscle weakness in the ICU and reported that 63% of individuals had diaphragmatic dysfunction, which was twice as frequent as peripheral muscle weakness and had a negative impact on weaning.

Parameters used to predict successful extubation during weaning from MV, such as peak expiratory flow (PEF) [12,13], are intimately related to respiratory muscle strength and airway protection capacity [14,15]. Kang *et al.* [16] identified a significant correlation between PEF and maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax). In addition, studies have shown that low PEF values are related to nine times greater risk of extubation failure [17].

In this condition, inspiratory muscle training (IMT) is a strategy used to strengthen the inspiratory muscles of critically ill adults [18]. Its benefits after prolonged MV and weaning have been proven in some studies [19,20,21]. In addition, a recent systematic review with meta-analysis showed that IMT is a viable and well-tolerated technique, capable of increasing inspiratory muscle strength by an average of 6 cmH_2O (95% confidence interval [CI], 5-8) [22].

A feasible and safe recommended duration to provide high-intensity intervention using a pressure limiting device in patients with ventilated pain is <7 days [18]. In Melo *et al.*'s preliminary study [23] on MV use for >7 days, IMT promoted respiratory muscle strengthening, but without significant results regarding weaning time and discharge from the ICU.

The study will be conducted using a linear mechanical loading device, which will be effective when used in the ICU [24,25,26], this equipment (POWERbreathe®) has minimal and specific pressure, by means of a calibrated spring, generating resistance to inspiration and adaptation of the inspiratory musculature [27]. The effects of early IMT in critically ill patients with this device have not yet been clarified; our main hypothesis is that an early attempt at IMT performed with a mechanical loading device will improve results of weaning in patients on MV and respiratory muscle strength.

Objectives

This trial primarily aims to evaluate the effects of early IMT in critically ill patients undergoing MV on weaning time, inspiratory muscle strength, length of stay in the ICU and weaning success rate.

Methods

Trial Design

A parallel-group, superiority randomised controlled trial, with concealed allocation and blinded assessments (single blinded), will be conducted according to the CONSORT recommendations [28,29]. A trained researcher, blinded to group allocation, will obtain signed written informed consent and measure

outcome measures at baseline and post-intervention (until weaning) (Figure 1). The examiner will be blinded to group allocation, and participants and the treating physiotherapist will be asked not to share any information about the intervention with the examiner. Participants will be randomly assigned to either (1) IMT combined with routine physical therapy (training group [TG]) or (2) routine physical therapy alone (control group [CG]) (Figure 2). The protocol for this trial was registered in the database for randomised clinical trials, ClinicalTrials.gov (NCT03758573) version 1.0, 29th November 2018. There is no plan for further trial modifications. The clinical trial protocol also follows the SPIRIT 2013 checklist [30].

Study Setting

The research will be conducted in the ICU of universitary hospital (Hospital Universitário da Universidade Federal do Vale do São Francisco - HU-UNIVASF; Petrolina/PE, Brazil).

Ethics/Governance

Ethics approval has been obtained from the Research Ethics Committee of the UNIVASF (REC-UNIVASF; N. 2.680.771), was gained on 12 July 2018. Written informed consent will be obtained from the participants or their relatives/responsible at the time of recruitment, including consent for evaluation and intervention procedures adopted in the research. Personal information will be coded to maintain and protect participants' confidentiality. At any time, the trial may be independently audited by the ethics committees.

Study population and eligibility criteria

The sample will consist of individuals of both sexes who meet the following inclusion criteria: (1) age ≥18 years; (2) intubated; (3) on MV for at least 24 hours; (4) in spontaneous modes of ventilatory flow; (5) without sedation for >12 hours; (6) functional level ≤3; (7) maximum inspiratory pressure (PImax) ≥20 cmH$_2$O; (8) mean arterial pressure ≥60 cmH$_2$O and ≤130 cmH$_2$O; (9) fraction of inspired oxygen ≤60 cmH$_2$O; (10) positive end-expiratory pressure ≤10 cmH$_2$O; (11) heart rate (HR) ≥60 bpm and ≤130 bpm; (12) respiratory rate (RR) ≤30 ipm; (13) peripheral oxygen saturation ≥90% and (14) temperature <38°C.

Participants with the following characteristics will be excluded: (1) under sedation, (2) administered vasoactive drugs, (3) spinal cord trauma, (4) progressive neuromuscular diseases, (5) previous tracheostomy, (6) terminal state, (7) pneumothorax, (8) unstable chest, (9) diaphragmatic injury, (10) ruptured eardrum and (11) postoperative pulmonary and abdominal surgeries. In addition, patients who cannot perform for IMT for two consecutive or four alternate days will be excluded from the trial.

Sample size and power calculations

The sample size was calculated using the G*Power V. 3.1.9.4 program [31], based on the F test, analysis of variance of repeated measures between independent groups. A type I error of 5%, power of 80% and effect size equal to 0.48, calculated from the means and standard deviations of a similar study that analysed weaning time from MV [32], gave a required number of 38 in total, with 19 participants in each group. Assuming an expected dropout rate of 10%, a target of 42 participants was set (21 participants per group).

When analysing the sample size of studies included in a recent systematic review [22], 23 (82%) studies had <50 patients and only five (18%) studies had ≥50 (mean sample size 34; standard deviation 23; minimum 6 and maximum 92). In view of this analysis, this feasibility study will hopefully contribute to decision-making around the clinical application of early IMT in critical patients.

Although this study is underpowered to detect the outcome measures, one may argue that including this outcome measure (weaning time from MV) will provide important feasibility data for future studies.

Participant identification, recruitment and informed consent

The main investigator will examine all ICU patients daily for study eligibility (Figure 2). Recruitment will be facilitated by the use of the evaluation form completed daily by physiotherapists, and this registration will allow the identification of eligible patients according to the pre-established criteria. During the screening visit, those responsible for eligible participants will be informed of the procedures for evaluations and interventions to be adopted in the research, all questions will be answered, and participants will be invited to sign the informed consent form.

The following information will be included in the informed consent form: "Ethical guarantees: To participate in this study you will not have any cost, nor will you receive any financial advantage; however, all expenses that may occur with the research will be repaired (refunded). Your right to compensation is also guaranteed (repair or compensation for any loss that may occur). You will receive full and immediate assistance, free of charge, for as long as necessary in case of damages resulting from the research and you can to refuse to participate and still refuse to continue participating in any phase of the research, without any prejudice".

Randomisation, allocation concealment and blinding

Patients will be randomly assigned to receive either routine physical therapy (CG) or routine physical therapy with IMT (TG). A randomisation sequence will be created using the website www.random.org, with a 1:1 allocation ratio using blocks of 10 participants. Allocation concealment will be achieved by means of sequentially numbered, opaque and sealed envelopes.

The randomisation sequence will be computer generated prior to study commencement by a trained research assistant, who will be not involved in the study, and maintained in randomised blocks in sequentially numbered sealed opaque envelopes. Eligible participants will be randomly allocated to either the control or experimental group, after the baseline measurements. The training therapist will be

responsible for revealing the contents of the sealed opaque envelopes and, therefore, for revealing the allocation.

After blinded assignment to interventions, outcome assessors and data analysts will also be blinded. They will not have access to the information of either the control or experimental group. Participants will be prohibited from saying anything about their treatment. Allocation will be revealed to the outcome assessors after the post-intervention evaluations and to data analysts after the statistical analysis. Data referring to the groups will be coded for blinding of the researcher who will perform the statistical analysis.

Plans for assessment and outcome collection will be prepared in which the assessors (blinded to the interventions) will perform assessments pre- and post-intervention, will be well trained for evaluation procedures and will be checked at the baseline for all outcomes. The data collection forms will remain with the main researcher.

Outcomes

The primary outcome is weaning time from MV (days) from baseline to the end-point. Secondary outcomes will be respiratory muscle strength (mmHg) (baseline and end-point), mortality (n) (end-point), length of stay in the ICU (days) (end-point) and successful weaning (n) (end-point). Respiratory muscle strength will be measured as PEF, PImax and PEmax. Successful extubation will be defined as maintaining spontaneous ventilation for at least 48 hours after the interruption of artificial ventilation [33].

Interventions

This article provides a detailed description of the background, target population and methodology of the IMT study, a randomised controlled trial investigating the effects of early IMT in critically ill patients undergoing MV using the POWERbreath® combined with routine physical therapy (TG) versus routine physical therapy alone (CG) on weaning time, inspiratory muscle strength, length of stay in the ICU and weaning success rate.

The study participants included will be assessed daily until discharge through routine ICU monitoring. The following haemodynamic parameters will be recorded at each session: HR, RR, peripheral oxygen saturation and systolic and diastolic blood pressure. As for ventilation parameters, the following markers will be observed: ventilation mode, volume, pressure, respiratory frequency, inspiratory time, positive end-expiratory pressure, inspired oxygen fraction and presence of acid/basic and/or oxygenation disorders by collecting arterial blood for gas analysis performed daily. To assess the level of consciousness, the Glasgow Coma Scale will be used [34].

IMT

IMT will occur in the TG using POWERbreathe® equipment (Medic, London, United Kingdom), according to the following parameters: load adjusted daily at 50% of PImax, three sets of ten repetitions with one-minute rests on the mechanical ventilator between each series, twice a day, with patients in bed at the bedside angle of 45°, while on MV. Adjustments in the IMT load will occur according to PImax values evaluated daily by the interventional physiotherapist [20]. Supplemental oxygen will be administered during IMT [35], and the endotracheal cuff pressure will be maintained at 30 mmHg during training [36]. If necessary, airway aspiration will be performed before the procedure.

Routine ICU care (common interventions to the both groups)

Both groups will remain under routine ICU physical therapy, consisting of respiratory and motor physiotherapy. Such routine care will include an individualised and supervised intervention programme, consisting of any of the following procedures: bronchial hygiene manoeuvers and pulmonary expansion therapy. Passive, assisted, active or resisted mobilisation and sedation will depend on the functional level of the patients [37]. There will be 10 joint mobilisations, prioritising diagonal and combined movements that favour patient functionality, in addition to a lower limb cycle ergometer for 30 minutes and functional positioning according to the protocol adopted at the institution.

The protocol will be discontinued if the patient has two or more of the following signs of respiratory failure or adverse events: RR >35 incursions per min; peripheral oxygen saturation <90%; HR >130 bpm; systolic blood pressure >180 mmHg or <90 mmHg and signs and symptoms such as agitation, sweating, altered level of consciousness and thoraco-abdominal asynchrony [21]. We do not anticipate problems with regard to adherence because the patients are hospitalised. Other relevant details of concomitant care is that the protocol will recommended not to use too much sedative in these patients, although use of sedatives will not be prohibited.

Oversight and monitoring

The trial will be overseen and monitored by co-investigators involved in the day-to-day running of the trial, who will meet weekly throughout the project. In addition, independent experts with relevant clinical research and statistical experience from HU-UNIVASF and Research Ethics Committee of the UNIVASF (REC-UNIVASF) will meet twice yearly to ensure data integrity and participant safety.

Despite the short duration of this trial, any modifications to the protocol that may impact the conduct of the study, the potential benefits for the patient or patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be approved by the Research Ethics Committee. The plans to communicate the trial results involve dissemination to the hospital and university and publication in journals and conferences.

All essential documentation and trial records will be stored in accordance with the applicable regulatory requirements, and access restricted to authorised personnel at HU-UNIVASF and the research group

(Research Group on Evidence-Based Practice). Trial documentation and data will be archived in an online repository.

Dissemination of information

The trial will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) checklist, and results will be disseminated in peer-review scientific journals. Important modifications to the trial protocol will be communicated to the funder, study investigators, HU-UNIVASF, REC-UNIVASF and trial registries.

Study status

At the time of initial manuscript submission, recruitment had already started for the trial. The study started in March 2019. The trial is recruiting participants but is paused due to COVID-19.

Statistical analysis

To verify the normality of the distribution, the Shapiro–Wilk test will be used. For comparisons of means between and within outcome groups, generalised estimating equations will be used, with its own syntax and linear distribution and when necessary, multiple comparisons will be performed using the Bonferroni test to identify differences. Categorical variables will be compared using the chi-square (χ^2) or Fisher's exact test where appropriate. Statistics such as difference of means (95% CI) and effect size (Cohen's d) will be calculated. Multiple imputation will be used in case of missing data. The intention-to-treat principle will be used in the final analyses. The statistical significance adopted will be 5%, and analyses will be performed using the statistical programme SPSS 22.0 (Statistical Package for the Social Sciences, Chicago, IL, USA).

Discussion

This randomised clinical trial aims to provide evidence of the effectiveness of early IMT in facilitating ventilatory weaning and inspiratory muscle strength in critically ill patients. The study will be conducted using the POWERbreath® mechanical loading device (Medic, London, United Kingdom). Although a training proposal with this equipment has already been described in the literature in athletes [24], outpatients [25] and patients with chronic obstructive pulmonary disease [26], to the best of our knowledge, no study has analysed early IMT using this device in mechanically ventilated patients.

Most studies involving ventilatory weaning with pressure threshold devices have been conducted with Threshold® (Philips, Amsterdam, Netherlands) or electronic devices. These studies were performed on patients under long-term MV, and training was started after the failed weaning [19,20,21].

As it is a low-cost device, POWERbreath® is believed to be an ally in the intensive care environment and can assist in the weaning process. We also believe that the results of this study have direct relevance to clinical practice and will provide valuable information on the investigated intervention, increasing the use

of evidence-based practices, improving care for critical patients and potentially leading to economic benefits by reducing in-hospital costs. In addition, it is hoped that this study can extract issues of interest that may not have been previously analysed, as well as reflections to improve future work in this field.

The development of the protocol has some limitations; evaluations will be carried out using an analogue manovacuometer, and both the physiotherapist who will perform the interventions and the patients will not be blinded.

List Of Abbreviations

bpm: beats per minute; CG: control group; HR: heart rate; HU: hospital univertary; ICU: intensive care unit; IMT: inspiratory muscle training; MV: mechanical ventilation; PEF: peak expiratory flow; PEmax: maximum expiratory pressure; PImax: maximum inspiratory pressure; REC: Research Ethics Committee; RR: respiratory rate; TG: training group.

Declarations

Ethics approval and consent to participate

All patients will provide written consent, prior to participation. This study has been approved (2.680.771) by the ethical review board of the Universidade Federal do Vale do São Francisco (UNIVASF), was gained on 12 July 2018.

Consent for publication

Not applicable.

Availability of data and materials

The data sets generated and / or analyzed during the current study will be available in the repository Harvard Dataverse, [https://doi.org/10.7910/DVN/JPTMH1]; or will be available to the corresponding author upon reasonable request.

This project contains the following extended data:

- CONSENT-FORM.pdf (informed consent form in English and Portuguese) <https://doi.org/10.7910/DVN/JPTMH1/PP5OQU>

- EVALUATION-FORM.pdf (evaluation form in English and Portuguese)

<https://doi.org/10.7910/DVN/JPTMH1/YXRHCC>

- SPIRIT-CHECKLIST.pdf - Standard Protocol Items: Recommendations for Interventional Trials - Checklist

<https://doi.org/10.7910/DVN/JPTMH1>

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

FBO, FOSM and RGSC participated in the conception and design of the study and performed the sample size calculation. FBO, JMM, HAR, PTFO will be the physiotherapists to perform the assessment and intervention. All authors read and approved the final version of the manuscript.

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Figures

	Study period				
	Enrolment	**Allocation**	**Post-allocation**		**Close-out**
Time point	$-t_1$	**0**	t_1	**Until weaning**	**Post weaning**
Enrolment:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
Interventions:					
Training group				→	
Control group				→	
Assessments:					
Patient data	X				
Primary and secondary outcomes variables			X		X

Figure 1

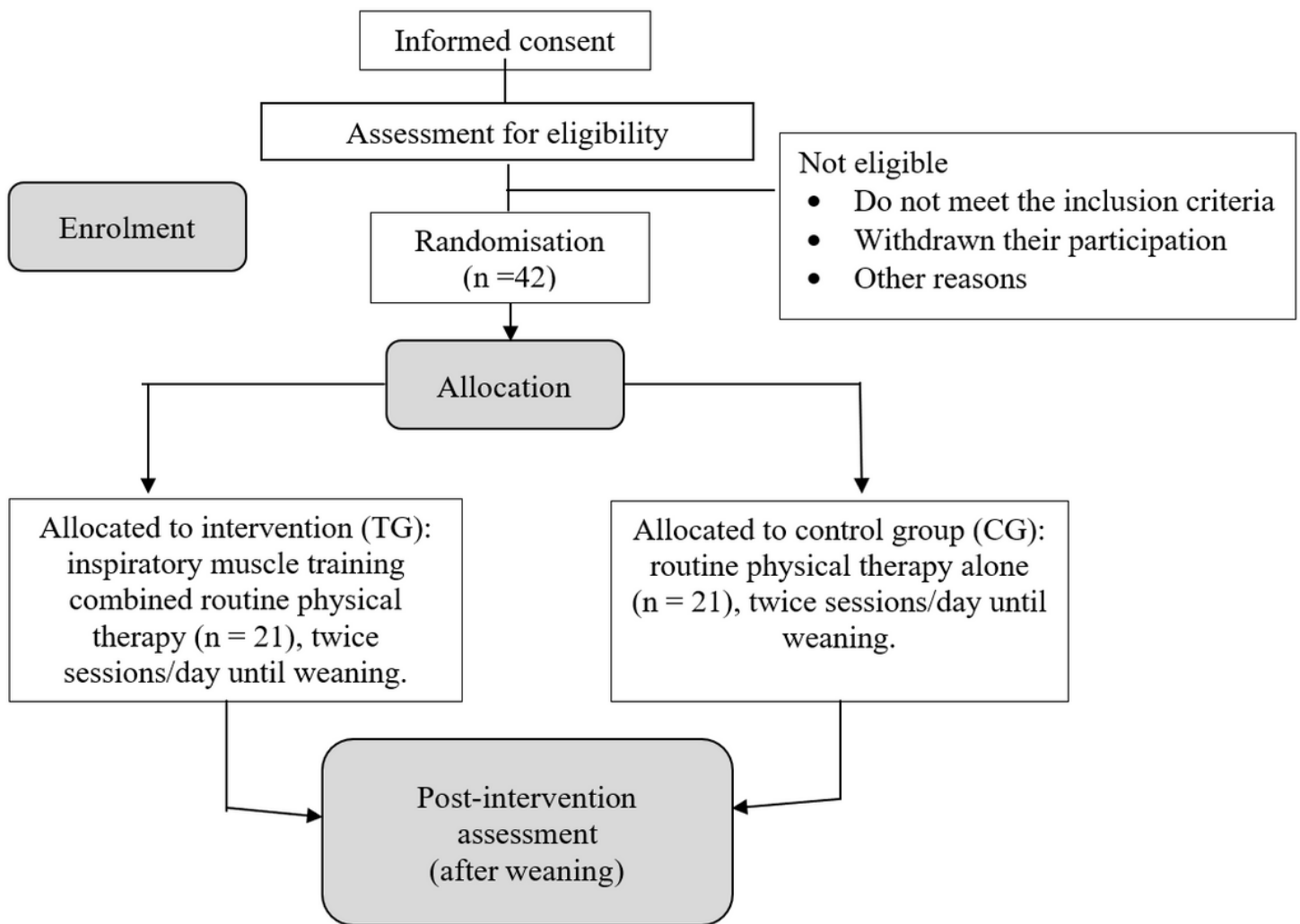Schedule of enrolment, interventions and assessments.

Figure 2

Flow diagram of the study. CG, control group; TG, training group.

Supplementary Files

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- CONSENTFORMportugueseenglish.pdf
- EVALUATIONFORMenglishportuguese.pdf
- SPIRITchecklist19022021.pdf