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Can inspiratory muscle training improve breathing characteristics in weaning failure patients?

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Woord Vooraf

Graag willen wij onze oprechte dank betuigen aan onze promotoren, Prof. Gosselink en Prof. Langer, voor het vertrouwen en de ondersteuning die we kregen bij het schrijven van deze masterproef. Zonder hun feedback, tips en motivatie had het niet mogelijk geweest om een dergelijk eindresultaat te bereiken.

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Situering

De huidige Belgische gezondheidszorg is zwaar belast met het financiële aspect van de zorgverlening. Het is een kwestie van de beste zorg toe te dienen op een manier zodoende dat het financiële klimaat van de zorg er niet onder moet lijden. Wanneer er specifiek wordt gekeken naar het ziekenhuismilieu ziet men dat een verblijf op intensieve zorgen gepaard gaat met een hoge verblijfskost. Des te langer een patiënt op intensieve zorgen moet verblijven, des te hoger de uiteindelijke kosten voor de maatschappij en voor de patiënt. Bij een aantal patiënten op intensieve zorgen is het langdurige verblijf te wijten aan het feit dat zij niet meer in staat zijn om zelfstandig te ademen. Dergelijke patiënten worden beademd om voldoende ondersteuning te bieden bij het ademhalingsproces. In bepaalde gevallen is het echter niet evident om de patiënt te ontwennen van de beademingsmachine. Vooral een verzwakking van de ademhalingsspieren speelt hier een pertinente rol in.

Doordat deze patiënten een langer verblijf op intensieve zorgen vereisen neemt ook de kost die deze patiënten bijdragen aan de Belgische zorgsector enorm toe. Daarnaast is het ook nadelig voor de gezondheid van de patiënt om een langere tijd gebonden te zijn aan de intensieve zorgen afdeling.

Dit onderzoek kadert binnen een groter project van de onderzoeksgroep Revalidatie bij Inwendige Aandoeningen van de Faculteit Bewegings- en Revalidatiewetenschappen van KU Leuven. Deze onderzoeksgroep richt zich voornamelijk op projecten bij patiënten met hartaandoeningen, longaandoeningen en patiënten opgenomen op intensieve zorgen. Deze studie bekijkt de invloed van hoge intensiteit krachttraining voor ademhalingsspieren op ademhalingsparameters bij patiënten opgenomen op intensieve zorgen waarbij ontwenning van de beademing moeizaam verloopt. Er wordt nagegaan of het doen van ademspiertraining een positief effect heeft op allerlei parameters die aantonen dat de ademspierkracht vooruitgang boekt. Het groter project integreert de uit deze studie vergaarde informatie en bekijkt de invloed van deze trainingen op het ontwennen van patiënten van mechanische ventilatie op intensieve zorgen.

Abstract

Introduction

Mechanical ventilation (MV) is often used in the intensive care unit (ICU) to assist a patient's breathing. This can lead to inspiratory muscle weakness and cause difficulties when weaning patients from MV. Although small, the proportion of patients that are considered 'difficult to wean' represent high costs for the healthcare system. Inspiratory muscle training (IMT) can have beneficial effects on breathing characteristics and respiratory strength. IMT can be conducted with different training modalities. Mechanical threshold loading (MTL) has been investigated with varying results. Tapered flow resistance loading (TFRL) is a relatively new training modality. Both training modalities have been investigated in the ICU but few studies have investigated high-intensity TFRL training in an ICU population.

Objective

This study aims to investigate the impact of high-intensity tapered flow resistive loading training on breathing characteristics in difficult to wean patients on the ICU.

Methodology

Patients experiencing weaning difficulties on either the surgical ICU or medical ICU were screened for participation. Patients with hemodynamic stability, adequate mentation and adequate oxygenation were randomly allocated into the control group or the intervention group. The control group underwent TFRL training at 10% of their maximal inspiratory pressure (Pimax) whereas the intervention group underwent high intensity TFRL training starting at 30% of the Pimax but adjusted daily to the highest tolerable load allowing for at least 70% of their FVC. Training sessions were performed daily for a maximum of 28 consecutive days. Each training session consisted of 4 sets of 6-10 repetitions. Breathing characteristics during the training sessions (tidal volume, power, work of breathing and inspiratory mouth pressure) and pre-training and post-training measurements such as Pimax and FVC were analyzed and compared between groups.

Results

After randomization, 16 patients were included in the control group and 11 in the intervention group. There was no significant difference in gender, age, length, weight and BMI between groups. Between group comparison of breathing characteristics resulted in significant differences in training intensity (load/PImax), pressure-time product, power ($p<0.01$) and work of breathing ($p<0.01$). No statistically significant difference was found in average tidal volume ($p=0.38$). High Intensity IMT resulted in somewhat larger improvement of Pimax (12.8 vs 15.4) but when compared to low intensity training the difference is not statistically different. High intensity IMT leads to a statistically significant improvement in FVC (0.1 L vs 0.4 L) compared to the control group ($p<0.05$). There was no statistically significant difference in compliance (67,3 % vs 72,7 % $p= 0.90$) between groups and there were no adverse events over the course of the study. There was no statistically significant difference in BORG scores for effort (4.3 vs 5.1, $p=017$), dyspnea (3.9 vs 4.3 $p=0.48$) and pleasantness (4.1 vs 4.0, $p=0.90$).

Limitations

The small study sample limits the power and external validity of this study. Further, the selected timeframe of 28 consecutive days ensures a different compliance for every patient in the study which can limit progress in breathing characteristics and respiratory strength.

Conclusion

High intensity TFRL training is safe and feasible in an ICU population experiencing weaning difficulties. Training compliance in the intervention group was 72,7% compared to 67,3% in the control group. High intensity TFRL leads to a significant increase in Power and Work of Breathing and improved forced vital capacity but not maximal inspiratory pressure. This could reverse respiratory muscle deconditioning due to critical illness, bedrest and mechanical ventilation.

Introduction

In the intensive care unit (ICU), mechanical ventilation (MV) is an important and life-saving part of the care given to patients. Approximately half of the patients admitted to the ICU require the use of MV[1]. The term weaning refers to the process a patient goes through to be liberated from mechanical ventilation. To achieve successful weaning many different training modalities have been tried[2]. Half of the time a patient spends being mechanically ventilated is comprised of weaning, with 80% of patients on MV being separated on the first separation attempt without difficulties[3]. Roughly 20% of mechanically ventilated patients experience difficulties during the weaning process[4]. This group of patients requires more than one separation attempt, longer duration of mechanical ventilation and significantly more resources. This population is often described as 'failure to wean' and poses great costs for healthcare services and challenges health care professionals[5,6].

Different aetiologies of 'failure to wean' have been identified in the literature. Imbalances between the load on inspiratory muscles in regular breathing and their maximal pressure generating capacity have been identified as possible origins of weaning failure[7]. Maximal inspiratory and expiratory pressures reduce following one or more weeks of mechanical ventilation. This led to the conclusion that there is a significant correlation between maximal inspiratory pressure (Pimax), maximal expiratory pressure (Pemax), vital capacity (VC) and medical research council scale (MRC) score indicating that ICU acquired weakness (ICUAW) may also impact respiratory muscle function[8]. MV itself can adversely affect the weaning process, weakening the diaphragm through inactivity. Low contractile activity in diaphragm muscle fibers is associated with a decrease in diaphragm muscle thickness and is found in patients requiring more extensive support, through higher ventilator driving pressure of MV.[9]. Placing a carefully selected load on the inspiratory muscles during MV can help counteract inspiratory muscle deconditioning[10]. Weakness of the diaphragm and accessory inspiratory muscles is widely seen as the cause of difficult separation from MV[3,11]. In conclusion, inspiratory muscle weakness and deconditioning are important factors contributing to weaning failure.

Since weakness of the respiratory muscles is considered as a major cause of weaning failure in patients in the ICU, a number of studies tried to target the respiratory muscles with the aim to influence breathing characteristics and therefore impact weaning success. Inspiratory muscle training (IMT) has been researched in a chronic obstructive pulmonary disease (COPD) population and showed a significant increase in inspiratory muscle strength when using a mechanical threshold loading device (MTL)[12]. IMT has been proven to have a significant effect on weaning success (71% compared 47%, P = 0,039)[13]. Percentages can vary greatly with weaning successes of up to 100% in the IMT group compared with 57% in the control group (P < 0,5). IMT using an MTL device significantly increased the probability of weaning success with a relative risk of 1.34 (95% CI 1.02 to 1.76)[14]. A systematic review with meta-analysis illustrates that respiratory strength expressed as Pimax is significantly increased by IMT[14] with the general conclusion favoring IMT. The results of IMT using MTL are not always positive. Sometimes IMT using MTL can lead to reintubation rates of 5 control patients versus 3 intervention patients (P = 0,39)[15]. The above-mentioned results are mixed and inconclusive to suggest that IMT with MTL positively affects the weaning outcome of a mechanically

ventilated patient in the ICU. New modalities need to be explored in a better-defined population.

To date, one can conclude that MTL is the most commonly used and researched training modality in patients with weaning failure. However, the results obtained by MTL are not unanimously positive. Recently a new way of placing a load on respiratory muscles has gained popularity, placing a tapered load according to the flow a patient generates. The relatively new way of loading is administered via an electronic device that provides tapered flow-resistive loading (TFRL) for IMT. MTL can be considered as isotonic muscle work of the diaphragm over a part of the range of motion (ROM). At a certain point, the load becomes too great for the inspiratory muscles and airflow into the lungs halts. As a consequence, only a part of the diaphragm ROM is trained. TFRL corresponds more with isokinetic muscle work due to the tapering of the load according to the flow of air into the lungs. A decrease in load towards the end of inspiration makes sure that the patient trains at higher lung volumes. This suggests that the diaphragm is trained over a more complete ROM when compared to MTL training. TFRL has already been used as a modality for IMT in a COPD population[16]. This study concluded that inspiratory muscle training at high intensity with TFRL yields a larger increase in inspiratory muscle strength when compared to MTL in patients with COPD. Recently TFRL was investigated in a randomized controlled trial on tracheostomized intensive care unit patients[17]. A significant increase in mean inspiratory pressure after IMT using a tapered flow-resistive loading device was found, however, there was no significant difference in time spent on mechanical ventilation between both study groups. To date, only one study has used TFRL for weaning failure patients in an ICU setting[17]. A small study sample and the used method (starting at lower intensities of training) suggest the need to further explore high-intensity IMT using the TFRL device in this specific population.

Therefore this study aims to investigate the breathing characteristics during high-intensity TFRL training in comparison to low-intensity training and the effects on maximal inspiratory pressure and vital capacity after the training period in difficult to wean patients.

Methodology

The methodology of this study is analogous to the already published study protocol of the IMweanT study[18].

Patients

Patients were recruited on the surgical and medical intensive care unit of the University Hospital Leuven. Patients were eligible for inclusion when termination of weaning was not achieved within 24 hours after the first separation attempt and when they could follow simple verbal instructions. Readiness to wean is based on the decision of an ICU physician taking the following criteria into consideration: (1) Resolution of the acute phase of the disease which required the patient to be intubated, (2) Adequate oxygenation PaO_2/FiO_2 150-200 with positive end expiratory pressure (PEEP) ≤ 5 - 8cmH_2O and fraction of inspired oxygen (FiO_2) ≤ 0.4 – 0.5, (3) Absence of fever (temperature <38°C), (4) Hemodynamic stability (heart frequency (HF) <140 bpm), (5) Stable blood pressure (BP), no or minimal vasopressors (dobutamine ≤ 5mcg/kg/min, norepinephrine ≤ 0.1µg/kg/min), (6) Absence of myocardial ischemia, (7) Adequate hemoglobin >7-10g/dl, (8) Adequate mentation and (9) Adequate cough[2,13]. When a patient is deemed ready a separation attempt can be conducted using no or limited support of mechanical ventilation[4]. If a patient with a tracheostomy can sustain this for 24 hours the separation attempt is successful, intubated patients undergo a spontaneous breathing trial (SBT) lasting 30-120 minutes with or without extubation[4].

In intubated patients a successful separation attempt is a spontaneous breathing trial (SBT), lasting 30-120 minutes, with or without extubation. Tracheostomized patients have undergone a successful separation attempt when spontaneous ventilation, without the assistance of mechanical ventilation, was endured for 24 hours or more.

Patients were excluded if they had a pre-existing neuromuscular disease, were hemodynamically unstable, suffered hemoptysis, a spinal cord injury above T8, skeletal pathology that impairs the movement of the chest wall or used any type of home mechanical ventilation support prior to hospitalization.

Written informed consent was obtained prior to participation in accordance with the 1964 Declaration of Helsinki. The study was approved by the local ethics committee (Ethische Comissie Onderzoek UZ/KU Leuven).

Design

This study is a parallel-group, randomized controlled superiority trial with a 1:1 allocation ratio. Patients, physicians, nursing staff and outcome assessors were blinded for group allocation. Blinding was achieved using sealed, numbered opaque envelopes generated by an independent researcher who played no part in this study. This researcher prepared opaquely sealed and sequentially numbered envelopes (80 intervention group envelopes and 80 control group envelopes). Patients are stratified for 2 factors known to interact with weaning success rates: Acute Physiology and Chronic Health Evaluation II (APACHE II) score and COPD. Patients were grouped and randomized into four groups: (1) APACHE II < 18 and COPD, (2) APACHE II >18 and COPD, (3) APACHE II <18 and no COPD and (4) APACHE II >18 and no COPD. Due to the stratification, the envelopes are divided into 4 piles of 40 envelopes containing 20

intervention group envelopes and 20 control group envelopes. In every pile containing 40 envelopes block randomization of 4 and 6 is applied to ensure an equal distribution of subjects in the control group and the intervention group.

Procedure

Patients in the intervention group underwent high-intensity training sessions of inspiratory muscle training (IMT). Patients performed 4 sets of 6 to 10 breaths with a minimum of 2 minutes rest between each set. Visual feedback on volume and flow was provided using a laptop (BreatheLink Software, HaB International Ltd, UK). Patients were trained 7/7 days, training sessions were interrupted if one of the following contraindications was present: intolerable symptoms of dyspnea or breathing discomfort, transcutaneous oxygen saturation < 85% (SpO_2) or if the subject starts to cough. The training was performed using the tapered flow resistance loading (TFRL) device (POWERBREATHE KH2, HaB International Ltd, UK).

High-intensity means the training starts between 30-50% of the maximal inspiratory mouth pressure (Pimax). The training load was adjusted daily to correspond with the highest tolerable load in terms of Pimax which still allowed the patient to reach a tidal volume of at least 70% of their respective vital capacity. At the end of the training session, patients were asked to evaluate perceived breathing effort and dyspnea on a 10-point BORG scale. These subjective parameters were also taken into consideration for adjusting training intensity.

Patients in the control group followed the same protocol as the intervention group but received low-intensity IMT sessions with a maximum load of 10% of Pimax. If $3cmH_2O$ corresponded to >10% Pimax an adapted TFRL device was used to train patients. This device was able to administer a lower training load than $3cmH_2O$ (POWERBREATHE Classic, HaB International Ltd, UK).

Training sessions were continued for a maximum of 28 consecutive days or until the patient was successfully weaned. The weaning process of patients transferring to other hospitals was followed and training was continued if possible.

Alongside IMT, patients also underwent a standardized early exercise program, 'Start to Move ASAP' involving passive/active mobilization, sitting in bed/chair and bedside ergometry or walking according to their clinical status. Maximum inspiratory pressure (Pimax), forced vital capacity (FVC) and peak inspiratory flow are measured weekly and taken into consideration for adjusting the training load. Rapid shallow breathing index (RSBI), respiratory rate (RR), heart rate (HF), SpO_2, blood pressure (BP) and tidal volume (VT) are measured daily.

Breathing Characteristics

Breathing characteristics were assessed during every training session. Average values derived from all breaths over all training sessions per patient were used for group analysis. For each patient, the number of training sessions that were underwent were added up per group and divided by the number of patients in the group. Compliance measures were obtained by dividing the number of training sessions a patient underwent by 28, as the selected time window for this study was 28 consecutive days following the start of IMT. For every training session, the load at which a patient trained was recorded. Mean load was obtained by dividing the sum of the

load per group by the number of patients in the group. The load was also expressed as a percentage of the baseline Pimax to illustrate the progression of the patients over the training sessions. For every training session the number of breaths a patient conducted in the training session, the respiratory rate during training, the time it took to breathe in, the ratio of time it took to breathe in over the total time of one respiration were recorded. An average measure of tidal volume during the training sessions was obtained by dividing the sum of all tidal volumes in one training session by the number of breaths in that training session. A normalized measure of tidal volume over baseline FVC was calculated to illustrate the progression of volumes over the training period. Peak flow and mean flow data were obtained by taking the largest flow during the training session and the sum of all flows over the number of breaths per training session respectively. Peak inspiratory pressure is the most negative value of pressure a patient reached during every inspiration. Mean inspiratory pressure is the average negative pressure a patient obtained during every inspiration. Power data for every breath were calculated by multiplying peak inspiratory pressure by the inspiratory flow that was generated during every breath. Work of breathing data was obtained by multiplying the total pressure of every breath by the tidal volume of every breath.

Outcome measures

Forced Vital capacity (L), Pimax (cmH_2O) and RSBI were selected as outcome measures. Pimax was measured using a unidirectional valve which allows expiration and is connected to a manometer (PFT Systems Pocket-Spiro) and a computer which generated pressure vs time plots. Patients were encouraged to breathe in as forcefully as possible for 25 seconds. This procedure was repeated until patients completed 3 sets with 2 minutes rest in between. The most negative value of the 3 sets was used for analysis. Forced Vital Capacity (FVC) was measured by connecting a spirometer (PFT Systems Pocket-Spiro) to the endotracheal tube or tracheostomy tube. Patients will be encouraged to breathe out as forcefully as possible until they reach residual volume (RV) followed by a maximal inspiration until total lung capacity (TLC) is achieved. Patients were able to follow the maneuver on a computer for feedback. This procedure was repeated at least 3 times with 2 minutes of rest in between. The best maneuver was selected for analysis. Assessing FVC provided other parameters such as: forced expiratory volume in 1 second (FEV1), Tiffeneau-index (FEV1/FVC), inspiratory capacity (IC) and peak expiratory flow (PEF). Peak inspiratory flow (PIF) was measured with the same spirometer as FVC. Patients were asked to breathe out as far as possible and then breathe in as much air as possible in the shortest possible amount of time. RSBI was measured before every training session. Subjects were positioned in a 45° upright position and asked to breathe as they normally would for 1 minute. Breathing data was collected using MEC spirometer software and a 1 minute time window was manually selected to calculate the RSBI.

Data Collection and processing

Tidal volume, inspiratory flow and inspiratory pressure data during training sessions were collected using MEC spirometer software. Pimax and VC were measured at the start, weakly and at the end of the training period.

Raw flow, volume and pressure data from the IMT sessions were processed into excel spreadsheets using SPIKE version 8.11 (CED Software). Parameters such as the number of breaths, inspiration time (Ti), inspiration time over total time (Ti/Ttot), peak and average flow, tidal volume, peak and average inspiratory mouth pressure, power and work of breathing were extracted out of SPIKE for every training session and used for statistical analysis of breathing characteristics.

Statistical Analysis

Outcome measures were tested for normal distribution using Kolmogorov-Smirnov tests and where appropriate parametric statistical measures (unpaired t-test) were used to compare both groups. If data were not distributed normally, Mann-Whitney U tests were used to analyze the outcomes between groups.

Inferential statistical measures between both groups were used to compare the change in vital capacity, change in Pimax, change in RSBI and breathing characteristics.

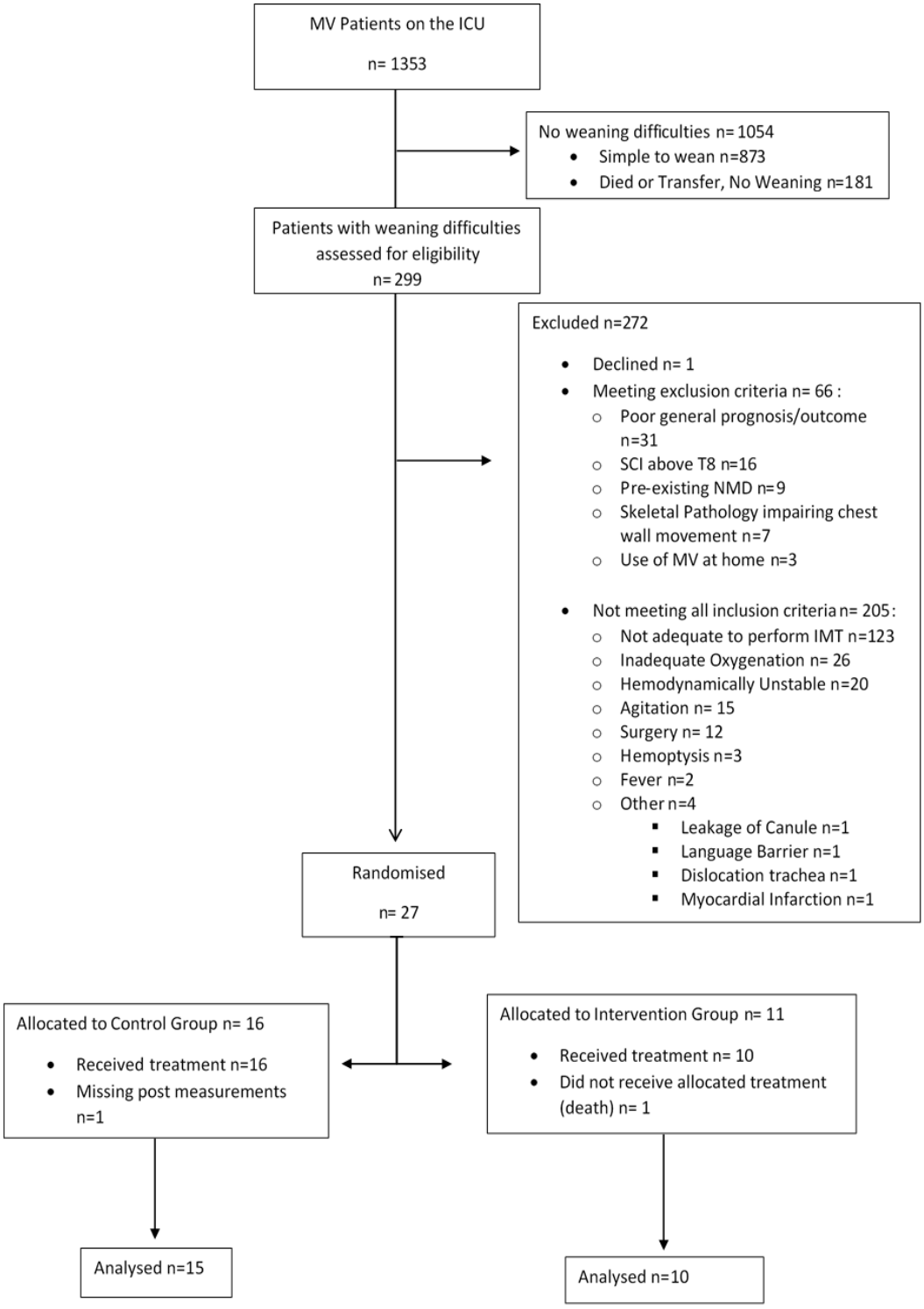
When it was not possible to assess an outcome post-intervention this data was seen as missing data.

The risk for type I error (α) was set at 5%. Statistical analysis was conducted using SPSS version 16 (IBM)

Results

During the running time of this study 1353 patients received MV on the ICU, 299 patients experienced weaning difficulties and were screened for participation in this study. 27 patients were included in the study, a flow chart of the study can be found in figure 1.

Figure 1: Flow chart of the Study



MV, Mechanical Ventilation; ICU, Intensive Care Unit; SCI, Spinal Cord Injury; NMD, Neuromuscular Disease; IMT, Inspiratory Muscle Training

Demographic and Clinical Variables

All demographic and clinical variables proved to have a normal distribution with the exception of the delay from the first failed separation attempt until the start of IMT (p=0.008).

Analysis of demographic variables showed that both groups were comparable at baseline. There were more women in the control group (50%) compared to the intervention group (36%) but the difference was not significant (p=0.696). Respiratory parameters proved to be comparable between both groups. A detailed depiction of all demographic variables can be found in Table 1.

Table 1 Demographic and Clinical variables of 10 intervention and 15 control subjects

Variable	Control Group (n=15)	Intervention Group (n=10)	P-value
Sex □Women, n (%) □Men, n (%)	 8 (50%) 8 (50%)	 4 (36%) 7 (63%)	0.69[a]
Age (years), mean (±SD)	66.4 (±7.8)	54.6 (±20.2)	0.09[b]
Length (cm), mean (±SD)	170.0 (±8.0)	169.4 (±6.8)	0.83 [b]
Weight (kg), mean (±SD)	65.5 (±20.6)	66.4 (±20.6)	0.92 [b]
BMI (kg/cm^2), mean (±SD)	21.9 (±6.1)	22.7 (±7.0)	0.75 [b]
COPD □No, n (%) □Yes, n (%)	 12 (75%) 4 (25%)	 7 (63%) 4 (36%)	0.68 [a]
APACHE II Score, mean (±SD)	21.3 (7.4)	21.0 (7.7)	0.09
Weaning Classification Baseline □Prolonged, n (%) □Difficult, n (%)	 11 (69%) 5 (31%)	 8 (73%) 3 (27%)	1.00 [a]
Breathing Modality Baseline □Endotracheal tube, n (%) □Tracheotomized, n (%)	 2 (12%) 14 (88%)	 2 (18%) 9 (82%)	1.00 [a]
Days between failed SA and start IMT (days), median (IQR)	21.0 (16.3-36.0)	30.0 (15.0-42.8)	0.58[c]
FVC baseline (L), mean (±SD)	1.0 (±0.6)	0.9 (±0.4)	0.45 [b]
%Pred FVC[19] (%), mean (±SD)	31.2 (±14.3)	23.4 (±11.9)	0.50 [b]
PEF baseline (L/s), mean (±SD)	1.0 (±0.4)	1.0 (±0.5)	0.89 [b]

PIF baseline (L/s), mean (±SD)	1.0 (±0.3)	0.9 (±0.2)	0.63 [b]
Pimax Plateau Baseline (cmH_2O), mean (±SD)	37.3 (±12.2)	33.5 (±13.9)	0.46 [b]
%Pred Pimax Plateau[20] (%), mean (±SD)	41.6 (±10.6)	34.5 (±14.3)	0.16 [b]
Peak Pimax Baseline (cmH_2O), mean (±SD)	46.4 (±12.1)	40.2 (±14.8)	0.24 [b]
RSBI Baseline (bpm/L), mean (±SD)	84.0 (±42.9)	94.7 (±24.6)	0.46 [b]

COPD, Chronic Obstructive Pulmonary Disease; APACHE, Acute Physiology, Age, Chronic Health Evaluation; SA, Separation Attempt; IMT, Inspiratory Muscle Training; FVC, Forced Vital Capacity; PEF, Peak Expiratory Flow; PIF, Peak Inspiratory Flow; Pimax, Maximal Inspiratory Pressure; RSBI, Rapid Shallow Breathing Index; % Pred, Percentage of Predicted value.

[a] = Fisher's Exact Test

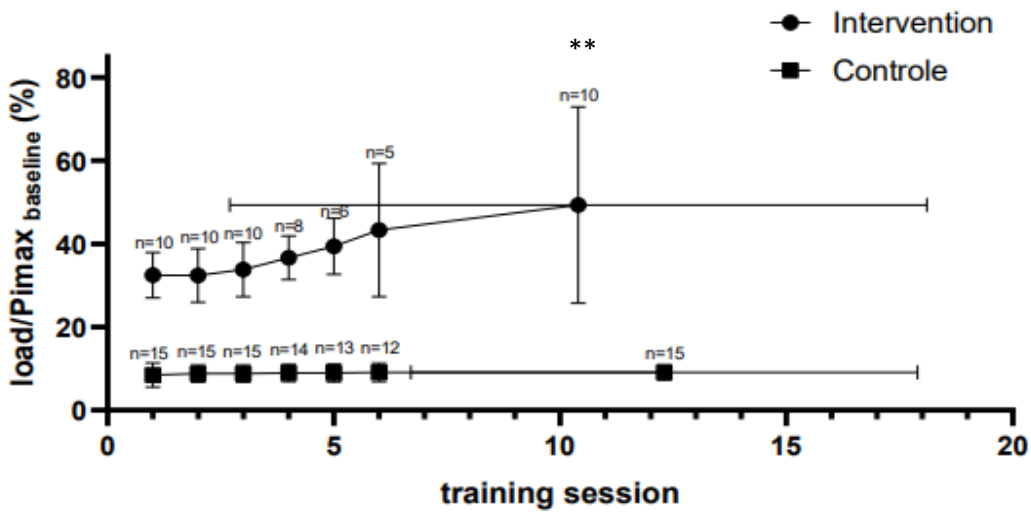
[b] = unpaired Sample t-test

[c] = Mann-Whitney U test

Breathing characteristics

All breathing characteristics proved to have a skewed distribution with the exception of the average number of training sessions. The compliance in both groups was not significantly different and during the time period of 28 days, there were no adverse events related to IMT. Indicating that IMT at higher intensities is safe and feasible in an ICU setting. The average maximal inspiratory pressure and average mean load in the intervention group proved to be higher than that of the control group. When compared to the control group, the invention group produces significantly higher power and average total work of breathing during the training sessions. For a more detailed depiction of the breathing characteristics, see table 2.

Figure 2: Progression of load corrected for Pimax



** Statistically significant difference between groups at $p<0.01$. This figure indicates that the control group trained at approximately 10% of the maximal inspiratory pressure (Pimax) whereas the training intensity of the intervention group varied daily between approximately 30%-50% of Pimax. The vertical bars represent the standard deviation of load/$Pimax_{baseline}$ (SD), the horizontal bars represent the standard deviation of the number of training sessions (SD).

Table 2 Average breathing characteristics of 10 intervention and 15 control subjects over the course of 28 consecutive days on the ICU

Breathing characteristics per training session	Control group (n=15)	Intervention group (n=10)	P-value
Average # Training sessions (days), mean (±SD)	12.3 (±5.6)	10.4 (±7.7)	0.23[a]
Average Compliance (%), median (IQR)	67.3 (54.8-81.2)	72.7 (63.0-75.0)	0.90 [b]
Average Mean Load (cmH_2O), median (IQR)	3.0 (3.0-3.0)	14.0 (8.4-16.5)	<0.01[b]**
Load/Pimax (%), mean (±SD)	7.9 (±1.9)	35.0 (±7.6)	<0.01[a]**
Average # Breaths, mean (±SD)	29.0 (±2.1)	23.7 (±4.0)	<0.01[a]
Average RR (bpm) , median (IQR)	12.9 (10.4-19.3)	12.0 (10.1-16.9)	0.17 [b]
Average Ti (s), mean (±SD)	1.2 (±0.5)	1.6 (±0.5)	0,93 [a]
Average Ti/Ttot (%), mean (±SD)	29.7 (±8.7)	30.2 (±8.5)	0.88 [a]

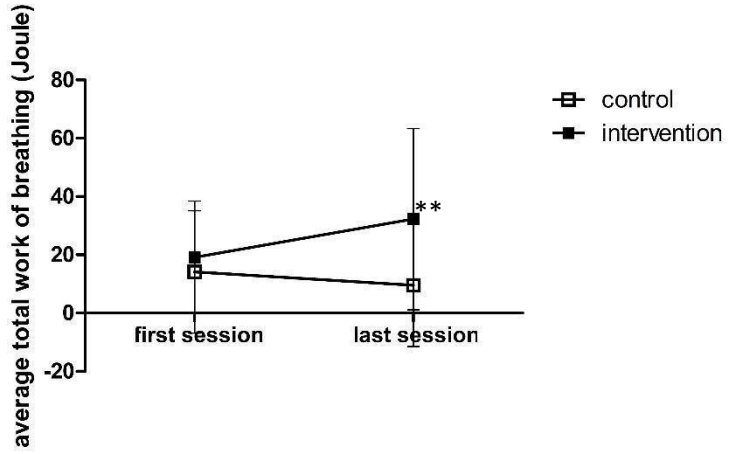
Average Tidal Volume (L), mean (±SD)	0.6 (±0.4)	0.6 (±0.3)	0.67 [a]
Vt/FVC (%), mean (±SD)	80 (±60)	90 (±70)	0.50 [a]
Average Peak Flow (L/s), mean (±SD)	1.0 (±0.3)	0.8 (±0.2)	0.14 [a]
Average Mean Flow (L/s) , mean (±SD)	0.5 (±0.2)	0.4 (±0.2)	0.06 [a]
Average Peak Inspiratory Mouth Pressure (cmH_2O), median (IQR)	5.2 (4.7-5.8)	14.6 (9.0-17.4)	<0.01 [b] **
Average Mean Inspiratory Mouth Pressure (cmH_2O), median (IQR)	4.0 (3.6-4.1)	8.2 (5.8-11.4)	<0.01 [b] **
Average PTP ($cmH_2O*s*min^{-1}$), mean (±SD)	1.2 (±0.3)	2.9 (±1.4)	<0.05 [a] *
Average Power (W), median (IQR)	0.4 (0.2-0.6)	1.0 (0.6-1.6)	<0.01 [b] **
Average Total Work of Breathing (J), median (IQR)	9.3 (5.0-15.7)	15.1 (9.7-27.1)	<0.05 [b] *
BORG Effort, mean (±SD)	4.3 (±1.4)	5.0 (±0.8)	0.17 [a]
BORG Dyspnea, mean (±SD)	3.9 (±1.6)	4.3 (±0.9)	0.48 [a]
BORG Pleasantness, mean (±SD)	4.1 (±1.9)	4.0 (±1.9)	0.90 [a]

* Groups significantly different at $P < 0.05$; ** Groups significantly different at $P < 0.01$; RR, Respiratory Rate; Ti, Inspiratory Time; Ti/Ttot, Time of inspiration over a total time of 1 respiration; PTP, Pressure Time Product. #, Number of; BORG, Scale to ranging from 0-10 to quantify perceived exertion.

[a] = Unpaired t-test

[b]= Mann-Whitney U-test

Figure 3: Comparison of total work of breathing between groups regarding the first and last training session



** Statistically significant difference between groups at $p<0.01$. This figure represents the total work of breathing subjects in both groups produced during the first and last training session. Both groups produced approximately the same work of breathing at the beginning of the training sessions but the work of breathing produced by the intervention group significantly increased over the course of the training sessions when compared to the control group. The vertical bars represent the standard deviation (SD).

Outcome Measures

All outcome measures proved to be normally distributed.

Unpaired t-tests of the remaining secondary outcome measures revealed that strength training yielded a statistically significant change in FVC 0.4320 (±0.34797) compared to 0.1333 (±0.36864) with endurance training ($p=0.05$). The intervention group also shows higher changes in Pimax and RSBI when compared to the control group with the difference not being statistically significant. Comparison of the BORG scores for effort, dyspnea and unpleasantness revealed that both strength training and endurance training are perceived as approximately equal in terms of effort, dyspnea and pleasantness.

A detailed view of the secondary outcome measures can be found in table 3

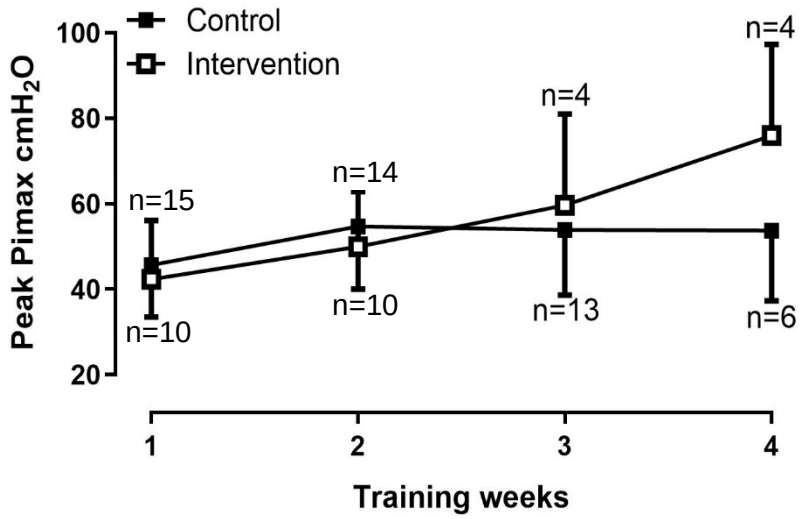
Table 3 Outcome measures of 10 intervention and 15 control subjects

Variable	Control Group (n=15)	Intervention Group (n=10)	P-Value
FVC change (L), mean (±SD)	0.1 (±0.3)	0.4 (±0.3)	0.05 [a] *
Peak Pimax change (cmH_2O), mean (±SD)	12.8 (±17.5)	15.4 (±16.3)	0.71 [a]
RSBI change (bpm/L), mean (±SD)	-8.7 (±26.9)	-26.9 (±27.5)	0.13 [a]

* Groups significantly different at P < 0.05; FVC, Forced Vital Capacity; Pimax, Maximal Inspiratory Pressure; RSBI, Rapid Shallow Breathing Index.

[a] = Unpaired Sample t-test

Figure 4: Evolution of Peak Pimax after 4 weeks of training following baseline measurements before the first training session



This figure illustrates the evolution of peak maximal inspiratory pressure (Pimax) over the course of 4 weeks of training. Included in the data points is the number of patients still training in the different groups of the study at various stages. At baseline (week 1) both groups have approximately the same average peak Pimax. The peak of maximal inspiratory pressure stays approximately the same in the control group, while the intervention group progresses. Note that the number of patients in the intervention group is drastically lower during week 3 and 4.

Discussion

This study focused on the effect of high-intensity TFRL training on breathing characteristics when compared to low-intensity TFRL training. The results of this study render that high intensity TFRL training leads to a statistically significant increase in average work of breathing and average power when compared to low intensity TFRL training. The difference in training intensity also resulted in a significant increase in FVC in the intervention group. Training intensity did not have a significant impact on peak Pimax measured weekly. During a period of 28 days, no patient experienced adverse events due to training.

As discussed in the results section, work of breathing (WOB) is significantly different between both groups. Two parameters are used to calculate WOB namely volume and pressure. As visible in table 3, there is no significant difference between both groups in tidal volume meaning that the difference in WOB can be attributed to the fact that the intervention group trains at significantly higher inspiratory pressures[16]. The capacity to generate higher pressures illustrates that training at higher loads leads to higher inspiratory strength. Higher inspiratory strength could result in an increase of respiratory capacity relative to respiratory load[21]. For patients in the ICU, this could reverse physical deconditioning due to bedrest and mechanical ventilation.

Power is largely dependent on the velocity of inspiration during IMT, generated by the patients[16]. In this study velocity of inspiration which corresponds to the inspiratory flow, was not significantly different between both groups. The power is significantly higher in favor of the intervention group. This could be attributed to the significantly higher inspiratory mouth pressure generated by the intervention group suggesting an increase in inspiratory muscle strength. This, in turn, could lead to a higher respiratory capacity which addresses deconditioning due to mechanical ventilation and bedrest[21].

This study found a significant increase in FVC indicating an increase in lung capacity through high intensity TFRL training. Since there was no statistically significant difference found in FVC in a COPD population using high intensity MTL and TFRL training[16], the intensity of training itself may provide an explanation for the resulting increase in FVC found in this study. Another possible explanation for the difference in results can be attributed to the study population. Patients on the ICU may have a lower respiratory capacity than patients with COPD. Starting training with a lower baseline capacity could mean that with correct training load a faster progression in volume can be achieved when compared to patients with COPD with a higher baseline capacity. A larger FVC may indicate a higher respiratory reserve for the patient[21]. This could mean that a patient breathes relaxed at rest and is able to carry out activities without getting shortness of breath.

The evolution of the Pimax measured weekly was not significantly different between both groups in this study. In the first 2 weeks, Pimax progresses at the same pace in both groups. During the last 2 weeks of training the intervention group progresses more and quicker than the control group, the difference may be statistically significant but is irrelevant due to a large difference in the number of patients still included in the different groups. After 2 weeks a larger proportion of patients in the intervention group is successfully separated from MV or discharged from the ICU compared to the control group. This successful separation may be due to high-intensity IMT but could also be affected by a better prognosis at baseline or differences

in age. The results obtained in this study are in contradiction with studies comparing IMT to standard physiotherapy[22] and those comparing different intensity MTL training[13].

Looking at the results for the BORG scores one can see that dyspnea and effort scores are higher in the intervention group than in the control group, although the difference is not statistically significant. Similar results were found when comparing BORG scores for effort and dyspnea between training with TFRL and MTL in a COPD population[16]. The scores for pleasantness are approximately the same in both groups but one would expect higher intensity training to be less pleasant than lower intensity training. A possible explanation for this outcome could lie within motivation through progression or variance of training variables[23]. Patients in the intervention group experience progress in training load and breathing characteristics which may make the training sessions slightly more pleasant.

A priori power analysis based on findings from previously conducted research revealed that in order to achieve a power of 80%, 45 patients per group would be needed. Weaning difficulties concern a small proportion of patients on the ICU[4] which lead to a sample size of 16 patients in the control group and 11 patients in the intervention group. This indicates that the sample size is a limiting factor of the study. A smaller sample size limits the power and external validity of this study making it difficult to detect a significant difference between the groups caused by the difference in training intensity.

This protocol aimed at a time window of 28 consecutive days of IMT on the ICU. Due to external factors i.e. surgery, disease exacerbation, dialysis, fatigue, it was not always possible to reach 28 days of training within the window of 28 consecutive days on the ICU for every patient. Although the average compliance was not significantly different it could be beneficial to analyze the samples when all patients have undergone the same amount of training days i.e. after every patient reaches 28 training days. A further limitation of this study lies within communication between the researchers, physiotherapists, ward nurses and medical staff. Communication and planning of the intervention need to be thorough to monitor the total load of all activities a patient undergoes on the ICU[24]. Patients who already underwent physiotherapy or periods of unassisted breathing may commence training sessions already fatigued which could lead to a decrease in tolerable training load for that day. In certain situations, the number of training sessions a patient underwent was cut short due to timing issues between medical staff and researchers with training sessions planned when patients were undergoing surgical procedures or investigations.

Weekly measurements of Pimax in this study were nonvolitional maximal efforts measured at the mouth. This type of measurement requires the cooperation and motivation of patients which can be influenced by the instruction given by the researcher, fatigue and comprehension[25].

Since high intensity TFRL training has a significant impact on the breathing characteristics of a patient, future research should aim to investigate the effect of high-intensity TFRL training on weaning outcomes, weaning duration and weaning related predictors such as RSBI and Pimax evolution[26] in critically ill patients experiencing weaning difficulties. Insights into motivating patients during IMT sessions could also be beneficial to identify crucial factors leading to maximizing the patient's effort every breath.

Conclusion

Inspiratory muscle training using high-intensity TFRL as training modality induces significant increases in power and work of breathing which are indicators of the load on the inspiratory muscles. Furthermore, no adverse events happened. This combined with compliance data indicates that training at higher intensities is both safe and feasible. Training at higher intensity also leads to a significant increase in FVC. These data are still preliminary and do not enable us to draw definitive conclusions.

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