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The Effect of Passive Cycle Ergometry Exercise on Dia-Phragmatic Motion of Invasive Mechanically Ventilated Critically Ill Patients in Intensive Care Unit: A Randomized Clinical Trial

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Abstract

Purpose: To assess the effect of cycle ergometry exercise in diaphragmatic motion of invasive mechanically ventilated critically ill patients admitted to an intensive care unit (ICU).

Methods: A randomized clinical trial was completed in the ICU of Hospital de Clínicas de Porto Alegre, Brazil. The patients were randomly selected to perform either conventional physical therapy or intervention (conventional physical therapy+cycle ergometry). Exercise on a bedside cycle ergometer was performed once a day, in passive mode for 20 min, from intubation to extubation, or until seven days.

Results: Diaphragmatic motion was measured by ultrasonography on intubation and extubation. Fourteen patients were selected to the conventional group (56.1 ± 23.0 yrs) and eighteen patients were selected to the intervention group (52.3 ± 22.7 yrs). Results demonstrated preservation of diaphragmatic motion on both conventional (0.61 ± 0.07 pre *vs.* 0.64 ± 0.12 post) and intervention (0.54 ± 0.06 pre *vs.* 0.68 ± 0.09 post) groups. Also, there was a positive correlation between variation of diaphragmatic motion and length of time receiving exercise protocol (r=0.031; p=0.915), and a negative correlation between variation of diaphragmatic motion and length of time receiving mechanical ventilation support (r=0.199; p=0.495) in the intervention group.

Conclusion: The diaphragmatic motion was persevered in both groups.

Keywords: Ergometry; Diaphragmatic

Introduction

Intensive care unit (ICU) patients present several comorbidities and are often exposed to prolonged immobilization, resulting in significant neuromuscular complications.[1,2] Difficulties in discontinuing ventilatory support can be found in 20% to 25% of mechanically ventilated patients, leading them to a variety of clinical situations, such as hypotension, hypoxia, and sepsis development [3-5]. Additionally, mechanical ventilation may induce diaphragmatic dysfunction by reducing the force production capacity of the diaphragm [6]. Diaphragmatic weakness is frequent in critically ill patients, having been associated with atrophy of both fast-twitch and slow-twitch myofibers, which can occur even after brief periods of mechanical ventilation. [7] This may all be associated with increased length of time of hospitalization and risk of mortality of ICU patients, therefore compromising their quality of life [5,8].

Muscle fiber loss, which is a consequence of mechanical ventilation and immobility, may lead to force reduction in respiratory muscles as well as in lower-extremity muscles [9] however early mobilization of critically ill patients may preserve muscle mass [2]. Therefore, exercising lower-extremity muscles with a bedside cycle ergometer has been used as an important tool, which can be attached to patients, allowing cycle revolutions of lower-extremity muscles [1]. This intervention has been demonstrated as a safe approach, which allows for passive or active modes, adjusted in accordance with each individual's ability [2,9,10].

A plethora of methods have been used for the assessment of diaphragmatic dysfunction, such as fluoroscopy and phrenic nerve electrical stimulation, although these are difficult practical clinical techniques to be performed [6,11]. Ultrasonography is a feasible tool to be performed, which may be available at the bedside for critical diagnosis of ICU patients [6,11,12]. Kim et al. [6] demonstrated that 29% of mechanically ventilated patients had diaphragmatic dysfunction, showing greater time in weaning from mechanical ventilation.

To our knowledge there is no study that has measured diaphragmatic function using ultrasound after cycle ergometry intervention. Therefore, the aim of this study is to measure the effect of

cycle ergometry exercise on diaphragmatic motion of invasive mechanically ventilated critically ill patients in ICU, as well as to verify the associations between diaphragmatic motion, and lengths of time receiving exercise protocol and mechanical ventilation support.

Materials and Methods

The present randomized controlled trial protocol was published in the Trials journal, [13] and the study was performed at the intensive care unit (ICU) of the Hospital de Clínicas de Porto Alegre (HCPA), being financed by the Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS), and funded by the Fundo de Incentivo à Pesquisa e Eventos (FIPE-HCPA). The study was conducted based on the Declaration of Helsinki of Good Clinical Practice, being registered on the randomized study system ClinicalTrials.gov (NCT 02300662). All patients and study participants signed the approved informed consent for participation in the study.

Study population

Men and women patients with age's ≥ 18 years, staying at HCPA's ICU, and receiving mechanical ventilation for 24 to 48 h of duration were included in the study. Patients should have at least up to one week of ICU stay. Patients that had neuromuscular or motor deficit issues, such as encephalic vascular accident, multiple sclerosis, and amyotrophic lateral sclerosis, myasthenia gravis, and Giullian-Barré syndrome were excluded from the study. The patients that were extubated in less than 48 h after inclusion in the study, and that had complications during the protocol, such as pneumothorax, deep vein thrombosis, pulmonary embolism, femoral vein Shilley catheter, need for reintubation, prolonged time in discontinuing ventilatory support (thee times fail in spontaneous ventilation test), body mass index (BMI) > 35 kg/m² and rise of back eschar over the calcaneus during the protocol were also removed from the study.

For the sample selection one researcher performed a daily screening for subjects that were eligible to participate in the study using the Clinical Hospital of Porto Alegre Management and Administration System (AGHWEB/HCPA). After that, identification, medical diagnosis, and current clinical condition were screened using the same electronic database. The individuals that were in charge of the patients that were selected in the database were invited to sign the Informed Consent Form (ICF).

Interventions

Patients were divided into two groups: Conventional group (CG) and intervention group (IC). The IC performed, besides physical therapy, bedside cycle ergometry to exercise lower-extremity muscles once a week supervised by a qualified researcher, following always the same assignment pattern. This was done either up to the day seven of mechanical ventilation (MV), until patients' extubation, or death. Patients were also divided as septic or non-septic within groups for comparisons. For bedside cycle ergometry exercise, participants were placed in supine position on a bed with head support elevated at 30˚. All exercises were performed bilaterally for knee and hips flexion and extension in passive mode (Flexmotor–Cajumoro, São Paulo, Brazil) for 20 consecutive min, and frequency of 20 revolutions per minute. All procedures were al-ways completed once a day in the afternoons. Before the conventional physical therapy session, one of the researchers of the study monitored for any clinical signs that patients could be demonstrating [9].

Always before and after exercise, the cycle ergometer was cleaned in accordance to the ICU routines, which was based on the Hospital Infection Control (CCIH-HCPA). Instructions were given to all patients before the cycle ergometry exercise, regardless of their level of consciousness or sedation. Sterilized wraps covered ankles of patients, in order to diminish any friction effect that could be caused by contact with the machine. Also, tapes were placed to maintain their ankles as closest to 90˚ of range of motion as possible.

The conventional physical therapy (respiratory and motor physical therapy) was done two times a day for 30 min. Patients' performed exercise routines prescribed by professional physical therapists, which consisted of diagonal patterns of proprioceptive neuromuscular facilitation for upper and lower extremities (two sets of 10 repetitions for each bilateral diagonal), and hand exercises for bronchial hygiene, such as vibrocompression, Ambu bag maneuver, and secretion aspiration when necessary.

Heart and respiratory rates, mean arterial pressure, peripheral oxygen saturation and ventilatory parameters were monitored during all appointments. After extubation, participants continued to be regularly assessed, as well as at-tending to conventional motor and respiratory physical therapy sessions until their transfer out of ICU.

Measurements

After completing 24 to 48 h of MV, and therefore being effectively included in the study, diaphragmatic motion of participants was assessed by ultrasonography on day one of inclusion and on day seven of MV. However, it was assessed before day seven when extubation was done before this period of time. A blind study assessment was performed by a researcher experienced in ultrasound use.

An ultrasound equipped with a linear probe (Ultrasound probe linear array 7.5 MHz-mode M; SONOSITE®, Washington, USA) was performed with subjects lied in supine position. A water-soluble gel was used to provide acoustic contact to the probe without compressing the dermal surface. The probe was placed between the midclavicular position and anterior axillary line, directed cranially, on a liver window analysis. Therefore, the probe was directed medially, cranially and dorsally, allowing the ultrasound beam to reach the posterior third of the diaphragm [12,14]. The diaphragm inspiratory and expiratory excursions were assessed in M-mode sonography. The inspiratory excursion was measured on the tracing between the baseline vertical heights of inspiration to the point of maximal height of expiration. The expiration excursion was measured on the tracing between maximal height of inspiration to baseline return [12,14].

Outcome measurements

Diaphragmatic motion was considered as the first outcome. Length of time receiving mechanical ventilation support, length of time of ICU stay and length of time of hospital stay, as well as successful extubation and number of deaths of patients were considered second outcomes.

Sample size calculation

The sample size calculation was based on a pilot study with 10 patients. The sample was calculated using WinPepi software (V. 11.43), which deter-mined a sample of n=14, using level of significance of 5%, power of 85%, and 2 repeated measures (pre and post).

Randomization

The patients were divided in randomized order into the conventional physical therapy group or the intervention group (conventional physical therapy+cycle ergometry). The randomization was done using the website www.randomization.com in blocks of ten patients. Only one researcher, which did not participate of data collection nor had previous knowledge of the study, was in charge of running the randomization.

Statistical analyses

The continued variables were described by either mean and standard deviation, or median and interquartile range. The categorical variable was de-scribed by absolute and relative frequencies. Shapiro-Wilk and Levene tests confirmed the normality and homoscedasticity of data, respectively. T-student for independent samples and Mann-Whitney tests compared means and medians between groups, respectively. Chi-Squared test or Fisher's exact test (when at least 25% of the cells had the expected frequency of <5) were used to analyze qualitative data. The model of generalized estimating equation (GEE),

with Bonferroni correction, was used to verify intragroup, intergroup and subgroup (septic versus non-septic) effects on muscle parameter changes. The association between variables was verified by Spearman coefficient correlation. Analysis of Covariance (ANCOVA) was used to control confounding factors, such as IMC, length of time receiving exercise protocol time and length of time receiving MV. A level of 5% ($p \leq 0.05$) was used to determine statistical significance. All analyses were done with SPSS 17.0.

Results

Thousand thee hundred and twenty one ICU patients were screened for eligibility, from May 2013 to November 2014. Within these, 1279 did not fit in the inclusion criteria. Initially, 42 mechanically ventilated patients were randomly selected to two groups (21 in each). However, throughout the study period there were patients with bad frequency on intervention sessions (reasons pointed out on Figure 1), which resulted in 32 patients completing the entire protocol of the study, in which 18 were from IG and 14 from CG (Table 1).

Analysed Variable	Intervention Group (n=18)	Conventional Group (n=14)	P Value[*]
Age, years, mean (SD)	52.3 (22.7)	56.1 (23.0)	0.65
Gender, n (%)			0.465
Female	13 (72.2)	8 (57.1)	
Male	5 (27.8)	6 (42.9)	
BMI, kg/m^2, mean (SD)	26.0 (5.8)	23.6 (4.4)	0.105
Laterality, n (%)			1
Right	16 (88.9)	13 (92.9)	
Left	2 (11.1)	1 (7.1)	
APACHE II, mean (SD)	23.7 (7.7)	23.8 (8.7)	0.981
Reason for ICU stay, n (%)			1
Sepsis	8 (44.4)	7 (50.0)	
Others	10 (55.6)	7 (50.0)	
Protocol length duration, days, mean (SD)	4.6 (2.4)	4.9 (2.5)	0.778

Table 1: Baseline characteristics (Values described in mean and standard deviation (SD), n and percentage; *t-student test for independent samples and chi-squared or fisher's exact test ($p \leq 0.05$); BMI: body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II).

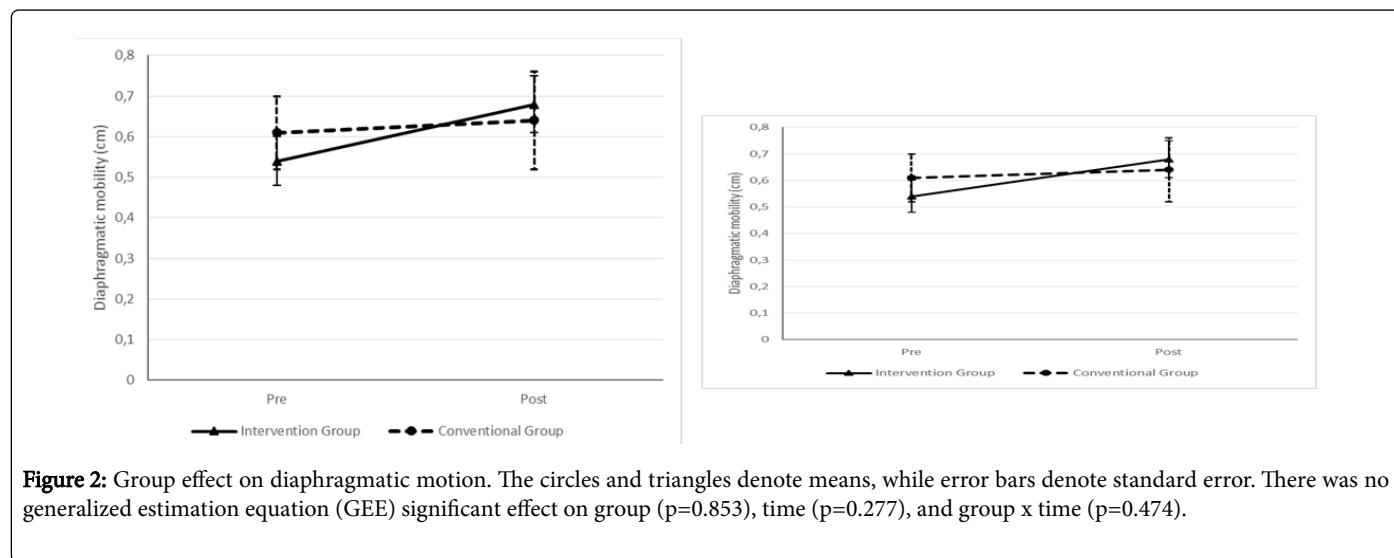**Figure 1:** Representation of study design.
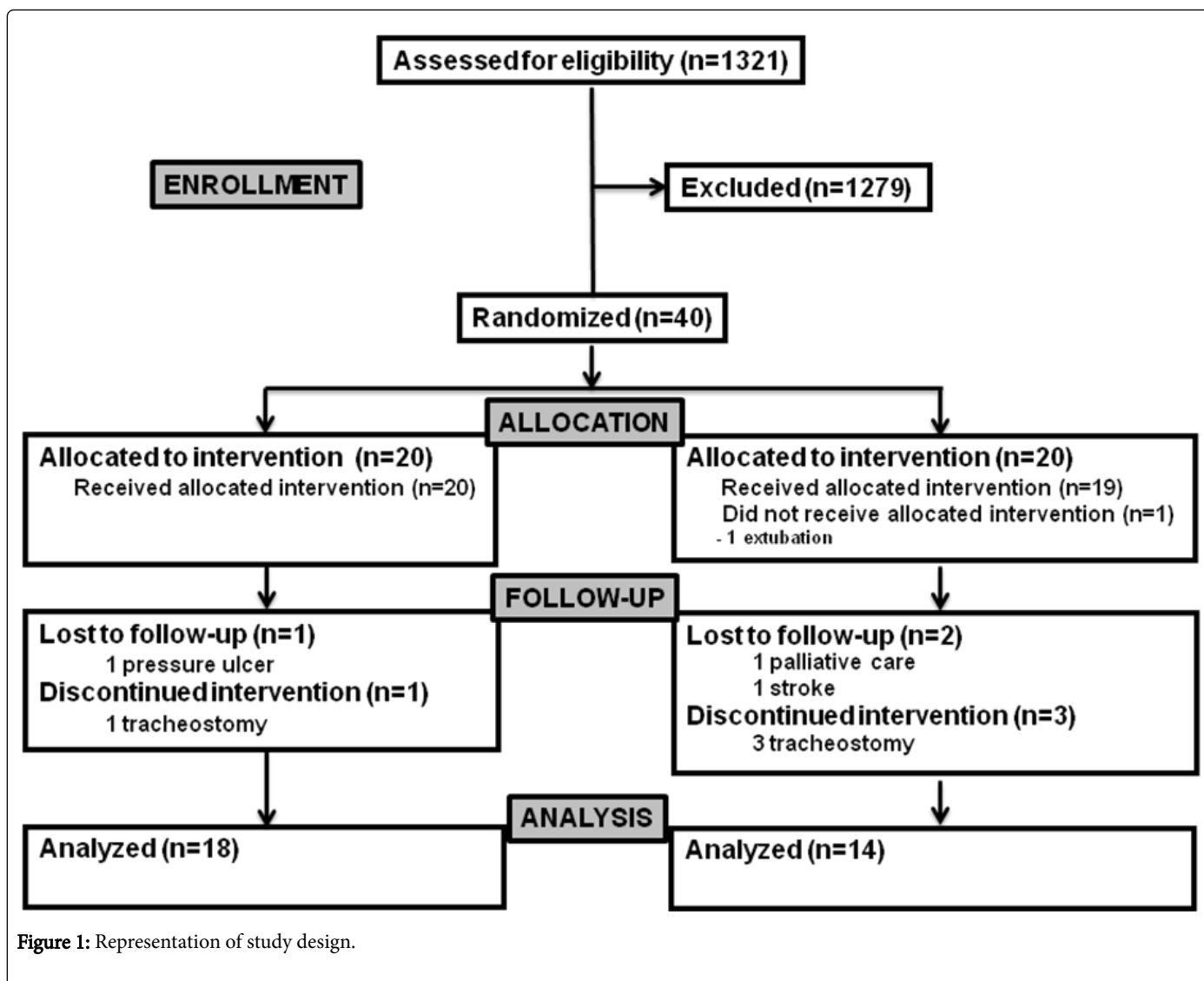
Outcomes

There was preservation of diaphragmatic motion in both IG and CG (Figure 2). However, no significant difference was found between groups on the length of time receiving mechanical ventilation support (p=0.905), length of time of ICU stay (p=0.619), and length of time of hospital stay (p=0.643), as well as successful extubation rate (p=0.411), and number of deaths (p=0.672) (Table 2).
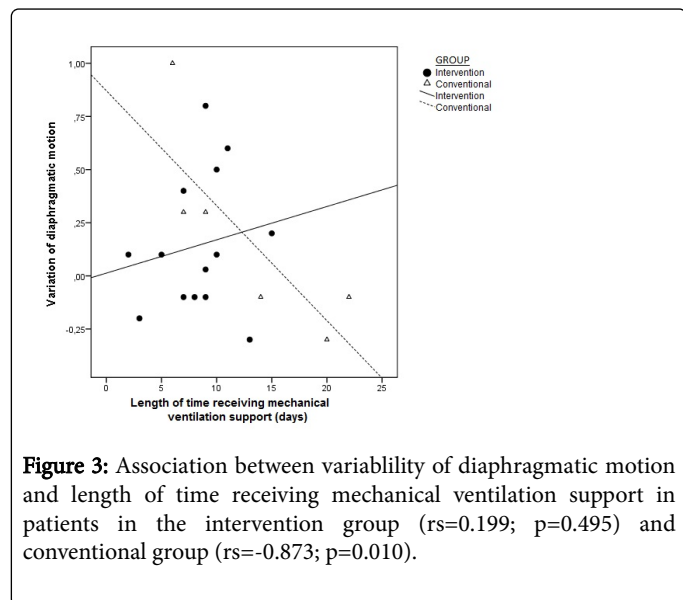
Analyzed variables	Intervention Group (n=18)	Conventional Group (n=14)	P value
Length of time receiving MV support, days, median (AIQ)	9 (7-10)	8 (5-13)	0.905
Length of time of ICU stay, days, median(AIQ)	11 (10-19)	15 (10-25)	0.619
Length of time of hospital stay, days, median (AIQ)	21 (15-37)	25 (17-36)	0.643
Successful Extubation, n (%)	12 (66.7)	12 (85.7)	0.411

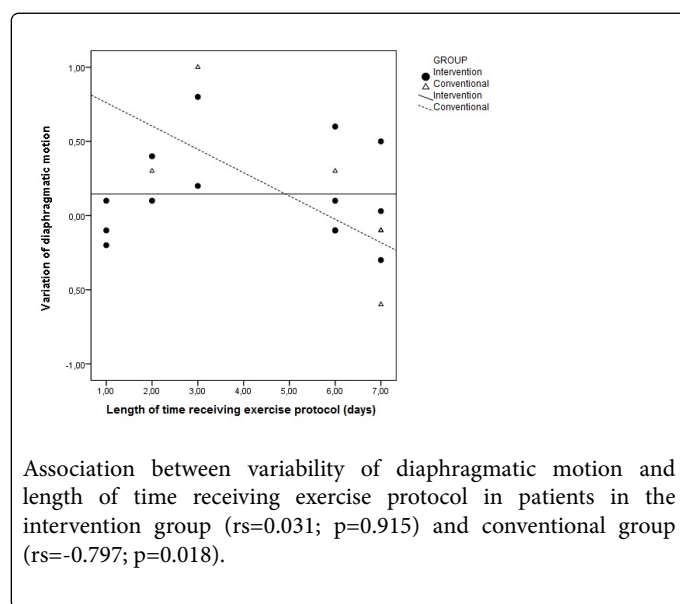| Deaths, n (%)	4 (22.2)	2 (14.3)	0.672

Table 2: Values denote length of time receiving mechanical ventilation support, length of time of ICU, length of time of hospital stay, successful extubation, and number of deaths (Values described in median and interquartile range, and n and percentage; *Mann Whitney and chi-squared or fisher's exact test (p≤0.05); MV: mechanical ventilation, ICU: intensive care unit).

Figure 2: Group effect on diaphragmatic motion. The circles and triangles denote means, while error bars denote standard error. There was no generalized estimation equation (GEE) significant effect on group (p=0.853), time (p=0.277), and group x time (p=0.474).

There was a non-significant positive correlation between diaphragmatic motion and length of time receiving mechanical ventilation support for IG (r=0.199; p=0.495), but a significant negative correlation between these variables for CG (r=-0.873; p=0.010) (Figure 3).

Figure 3: Association between variablility of diaphragmatic motion and length of time receiving mechanical ventilation support in patients in the intervention group (rs=0.199; p=0.495) and conventional group (rs=-0.873; p=0.010).

Similarly, there was a non-significant positive correlation between diaphragmatic motion and length of time receiving exercise protocol for IC (r=0.031; p=0.915), but a significant negative correlation between these variables for CG (r=-0.797; p=0.018) (Figure 4).

Association between variability of diaphragmatic motion and length of time receiving exercise protocol in patients in the intervention group (rs=0.031; p=0.915) and conventional group (rs=-0.797; p=0.018).

The vital signs and ventilatory analyses demonstrated that there was stability during interventions, and no occurrence of adverse events during the period of technique applications.

Discussion

The main finding of this study was that there was preservation of diaphragmatic motion on patients of both groups tested, who performed either only conventional physical therapy or physical therapy together with cycle ergometry exercise. Also, there was a direct correlation between variation of diaphragmatic motion and length of time receiving exercise protocol, and between variation of

diaphragmatic motion and length of time receiving mechanical ventilation support in the intervention group. However, this association was not found for the conventional group. Additionally, there was no group impact on the length of time receiving mechanical ventilation, successful extubation rate, and number of deaths, length of time of ICU stay and length of stay of hospital stay. The diaphragmatic atrophy during invasive mechanical ventilation is correlated eat severity of weakness acquired by the patient and the severity of the condition is associated with the duration of mechanical ventilation [15].

ICU patients, especially those receiving continued mechanical ventilation support, are exposed to several comorbidities. Diaphragm contractile dysfunction may lead to weakness in a consequence of increased weaning time [16]. Therefore, early mobilization may preserve peripheric and respiratory muscle mass [16]. Previous studies have demonstrated that early mobilization using a bedside cycle ergometer is a safe and feasible exercise tool in critically ill patients, being effective in improving their functional capacity and muscle strength [9]. However, we are not aware of any other study that has investigated the impact of the use of this exercise tool on the diaphragm.

We believe that critical ill patients without any kind of early mobilization may have several issues regarding immobility, particularly related to diaphragmatic dysfunction. However, in our study we did not find any statistical differences for this variable between groups when comparing pre and post interventions. Mechanically ventilated patients that do not perform early mobilization may decrease muscle strength by 25% from 4 to 7 days of hospital stay. This may lead to increased mortality and oxygen demand, negatively influencing patients in weaning from mechanical ventilation [9,10,17,18]. It has been previously reported that healthy subjects who were immobilized in bed for ten days reduced quadriceps strength from 1% to 1.5% for each day of immobilization, and this magnitude was even greater in elderly patients [18]. Several factors can influence on muscle weakness, such as malnutrition, prolonged immobilization, increased inflammatory cytokines, and neuromuscular abnormalities. Therefore, bed immobility associated to clinical status may lead to decreased muscle mass, especially in the lower extremities [2].

In addition, the muscle can occur with decreased muscle protein synthesis, increased muscle catabolism. These changes can manifest as reduzidaárea muscle cross section and decrease in contractile force. Furthermore, there is a general change of muscle fibers of slow twitch (type I) for fast-twitch (type II), leading to reduced endurance. Immobility can also increase the production of pro-inflammatory cytokines and reactive oxygen species, resulting in muscle proteolysis, with a net loss of muscle protein, and subsequent muscle weakness [19].

In our study no alterations were found on patients' vital signs or ventilatory parameters. The use of early mobilization has been currently more used for critically ill patient's rehabilitation [20]. In a recent study, a single 20 min cycle ergometry exercise on day 5 after ICU admission was tested in variables such as cardiac output, systemic vascular resistance, central venous blood oxygen saturation, respiratory rate and tidal volume, oxygen consumption, carbon dioxide production and lactate levels [21]. The authors considered bedside cycle ergometry exercise as safe, because no significant alterations were found in hemodynamic, respiratory or metabolic variables in these patients [21]. Similarly, in another study using passive exercise in

mechanically ventilated patients, no differences were found in respiratory rate, mean arterial pressure, and oxygen saturation during exercise [22]. Latest study examined the safety of using the cycle ergometer in the ICU and reported that the device is safe and feasible for use, needing more study to prove the same [23]. In our study we used ultrasound, because this is an important tool for diaphagm motion assessment, as well as simple and feasible to use. Kim et al. found that ultrasonography of diaphagm may be useful in predicting delayed weaning failure [6]. It also identified that patients with diaphagmatic dysfunction also presented prolonged mechanical ventilation. Therefore, ultrasonography may be a valuable tool to be used in the ICU in patients that have difficulty in weaning [6]. Grosu et al. demonstrated that mechanically ventilated patients may have decreased muscle thickness leading to diaphagmatic dysfunction [24]. These measurements could help on weaning of patients as well as to screen respiratory muscles function during the period mechanical ventilation. This study also identified that diaphagm muscle thinning starts within 48 h of beginning of mechanical ventilation, which may affect pulmonary function [24].

We did not find any differences on the length of time of hospital stay and length of time of ICU stay between groups. This is not in accordance to Brahmbhatt et al. since they found that patients that received an early mobilization rehabilitation exercise program had shorter ICU stay, reducing hospital costs, compared to patients receiving only standard care. Early mobilization patients also had more ventilator-free days and faster hospital discharge com-pared with standard care [25]. In our study, both groups received intervention exercise protocols, which may have lead to no significant differences when outcomes were compared. Schweickert et al. demonstrated that 59% of patients that performed early mobilization had better functional outcomes at hospital discharge. They also had more ventilator-free days compared to patients with standard hospital care [25]. These studies have demonstrated the importance of early mobilization on critical ill patients, regardless of the use of cycle ergometry exercise [25,26].

A few studies have found increased quadriceps muscle mass and strength after early cycle ergometry exercise in mechanically ventilated patients compared to patients receiving only daily standardized exercise, but with no differences regarding length of hospital stay or mortality between groups [9]. This demonstrates the importance of conventional physical therapy in patients in order to reduce muscle weakness [9,27]. Patients that have received early mobilization shortly after ICU admission had preservation of physical abilities, functional outcomes, and length of time of ICU stay. However, although scientific literature has reported that early mobilization is a safe and important tool for health of mechanically ventilated patients, the daily implementation of this practice in hospitals is still a big challenge [20, 28].

In a study with patients who required mechanical ventilation over 48 h, spontaneous breathing trial identified that those who presented diaphragm dysfunction had prolonged mechanical ventilation. Similar to our study, an ultrasound in mode M was used for these measurements [6]. In our study, there was an indirect correlation between diaphragmatic motion and length of time receiving exercise protocol, and between diaphragmatic motion and length of time receiving mechanical ventilation support in the conventional group. There was also a direct correlation between these variables in the intervention group. This demonstrated that patients with reduced diaphagmatic motion remained more time in mechanical ventilation

and had prolonged weaning time in the conventional group. Several investigations have suggested that early mobilization is important for critical ill patients with prolonged mechanical ventilation, which leads to pulmonar function improvement, reducing length of mechanical ventilation, as well as ICU stay [1,9,29].

Previous reports have also used bedside cycle ergometry in ICU patients, using methods similar to the ones we used, but including mobilization after sedation and weaning. Burtin et al. concluded that early exercise training promotes enhancement of functional exercise capacity, functional status, and muscle force at hospital discharge [9]. Therefore, the performance of this proto-col until hospital discharge may be important for more precise outcomes.

A recent literature review assesses that the loss of muscle strength is associated with a higher tempode mechanical ventilation, ICU stay, hospital stay and increased mortality, so the authors emphasize the importance of new studies that contribute to the prevention of this weakness [30]. The length of time of exercise protocol (7 days), as well as the time and frequency per intervention session are possible limitations of our study, and may have influenced our results. Future research with greater length of time of exercise protocol during the entire ICU stay of patients could be important to answer remaining questions of this study.

Therefore, our results demonstrated that diaphragmatic motion was pre-served in both groups, and adding a cycle ergometry exercise did no alter our examined outcomes. Additionally, there was an association between the variation of diaphragmatic motion and length of time receiving exercise protocol, and between variation of diaphragmatic motion and length of time receiving mechanical ventilation support in the intervention group, during the acute phase of patients stay in ICU.

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