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Original Article

# Inspiratory Muscle Training Prevents Diaphragmatic Atrophy in Mechanically Ventilated COVID-19 Patients.

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## ABSTRACT

**Background:** Unloading the diaphragm by mechanical ventilation results in diaphragmatic dysfunction and atrophy, a condition recognized in critical care settings as ventilator-induced diaphragmatic dysfunction (VIDD). This condition contributes to prolonged mechanical ventilation, extubation failure and higher risk of mortality.

**The aim of The Study:** The current study aimed to investigate the effectiveness of inspiratory muscle training in preventing or reversing diaphragmatic atrophy in mechanically ventilated COVID-19 patients.

**Materials and Methods:** 55 intubated, mechanically ventilated patients with hypoxic respiratory failure due to COVID-19 were randomly assigned into study (n = 32) and control (n = 23) groups. The former received inspiratory muscle training with the routine physiotherapy programme and the latter received routine physiotherapy only. Diaphragmatic thickness was measured and compared in both groups using ultrasonography.

**Results:** In the study group, diaphragmatic thickness at end of inspiration and expiration significantly increased by 14% and 8% respectively ($p < 0.001$). The increase in thickness fraction for this group (7.5%) was statistically insignificant ($p > 0.05$). In the control group, there was a significant decrease in all three parameters ($p < 0.001$).

**Conclusion:** Inspiratory muscle training by adjusting the ventilator's trigger sensitivity is a safe, effective and feasible method that can successfully prevent diaphragmatic atrophy in mechanically ventilated, COVID-19 patients.

**Keywords:** Diaphragmatic Dysfunction; Mechanical Ventilation; Diaphragmatic Atrophy; ICU Rehabilitation; COVID-19.



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* Main subject and any subcategories have been classified according to the research topic

## INTRODUCTION

The diaphragm is the main respiratory muscle that contributes to 70% of the tidal volume achieved in quiet breathing [1]. It is also more than just a muscle of respiration; it participates in a number of physiological processes such as cough and expectoration, emesis, swallowing, urination, and defecation [2]. It also plays an important role in facilitating venous return and lymphatic drainage and it regulates visceral actions by contributing to the intra-abdominal and intra-thoracic pressures [3,2].

From an anatomical perspective, the diaphragm is described as a dome-like muscular sheet that is attached to the thoracic wall by: a] costal b] sternal and c] vertebral attachments. Because the diaphragm is convex upward, it comes in apposition with the lower six ribs. This area of is known as zone of apposition [ZOA] [4]. From a functional perspective, the diaphragm is responsible for maintaining continuous, rhythmic and interrupted breathing. This is why the majority of its fibers are type I, slow-twitch fibers that are highly fatigue resistant [5].

Percentage of type-I [slow-twitch fibers] in the adult human diaphragm is approximately 55%; while percentages of type-IIa and type-IIb [fast-twitch fibers] are 21% and 24% respectively. In general, fast-twitch muscle fibers are less resistant to fatigue than slow-twitch fibers [4,5].

Muscle weakness and muscle atrophy in Intensive Care Unit [ICU] are two serious complications that physio-therapists face in critical care settings, and the diaphragm is not an exception; diaphragmatic dysfunction refers to loss of diaphragmatic force that may be partial [weakness] or complete [paralysis]. This dysfunction results in reduction of the individual's inspiratory capacity and endurance [5].

As a matter of fact, prolonged physical inactivity results in wasting and weakness of all limb and respiratory muscles. This disuse muscle atrophy occurs by several mechanisms, including alteration in protein turnover and disruption of redox signaling [6]. However, this atrophy occurs much earlier in the diaphragm than in other muscles based on the co-existing morbidities, [7] while wasting of limb muscles is known to be a slower process that occurs gradually during ICU stay [8].

Several factors can cause diaphragm weakness in ICU. The first factor is inactivity which leads to decline in all muscle performance including the respiratory muscles. This state is known as ICU-acquired muscle weakness [9]. Infection and the catabolic state also induce significant diaphragm weakness, in addition to other factors such as azotemia, hyperglycemia, and low systemic albumin levels which are considered serious risk factors leading to the development of respiratory muscle weakness [10].

Mechanical ventilation is also a responsible factor that directly leads to diaphragmatic dysfunction known as ventilator-induced diaphragmatic dysfunction [VIDD] [11–13].

Mechanical ventilation [MV] is a life-saving intervention, frequently used in ICU to maintain adequate oxygenation and alveolar ventilation in patients with respiratory failure and in a number of metabolic, cardiac and neurological conditions [9,14,15].

Although the use of MV helps critically ill patients survive, the prolonged use of MV contributes to a number of reversible and irreversible complications [16]. Prolonged MV is also associated with rapid diaphragmatic weakness due to myofiber atrophy, contractile dysfunction, sarcomeric disruption, intracellular lipid accumulation, and mito-chondrial dysfunction [11–13,17].

Observational studies have revealed that atrophy of the diaphragm is more prominent in patients who require high support modes such as mandatory and support modes of mechanical ventilation [6,18]. The use of the continuous mandatory ventilation [CMV] modes lead to rapid alteration in the structure and contractile function of the diaphragm. It also promotes oxidative injury, leading to diaphragmatic atrophy and weakness that occurs within 24 hours after mechanical ventilation [14]. A previous study reported that organ donors demonstrated rapid-onset loss of diaphragmatic thickness only 18–69 hours after mandatory ventilation [6]. Ventilator-induced diaphragmatic dysfunction worsens prognosis, prolongs MV duration and increases risk of extubation failure, and thus, increases the risk of mortality [14,19,20].

Recently, early rehabilitation in critical care units has been effective in shortening ICU and hospital stay, improving patients' physical performance, capacity, function and facilitating hospital discharge [6]. It is documented that prolonged mechanical ventilation leads to increased cost of hospitalization, poor prognosis, reduced quality of life after liberation from mechanical ventilation and even after discharge as well as an increased risk of complications and mortality [21,22]. Therefore, critical care physical therapists must give serious consideration to preventing and treating ventilator-induced diaphragmatic dysfunction as a goal of the early rehabilitation programme [6,14].

Inspiratory muscle training is considered a low-cost, evidence-based rehabilitation intervention that can be applied with different parameters based on every patient's individual condition [16,21].

In mandatory and support modes of MV, the diaphragm is unloaded by the mechanical ventilator. In light of this fact, all inspiratory muscle training protocols aim at placing a load on the inspiratory muscles –namely the diaphragm– in order to oppose the catabolic effects of diaphragm inactivity, thereby improve fiber activation, cross-sectional area, and contractile force [16,21,22].

In previous literature, different methods have been identified to load inspiratory muscles. These methods included isocapnic or normocapnic hyperpnea, inspiratory resistive training, threshold pressure and flow training using adaptors and external devices as well as adjustment of ventilator trigger sensitivity [20–24].

Ultrasound of the diaphragm is used to assess diaphragmatic function in a variety of respiratory conditions including asthma, cystic fibrosis, COPD, interstitial lung disease, and diaphragmatic paralysis [5]. It was found superior to other techniques because it is noninvasive and does not employ ionizing radiation. It is also feasible, reproducible, repeatable, and affordable with high inter-observer agreement [16]. It also has high sensitivity [93%] and specificity [100%] for diaphragmatic neuromuscular disease [25].

In the near future, ultrasonography of the diaphragm will have new applications in the diagnosis and monitoring of diseases and interventions, such as rehabilitation [5,25,26]. It is also a promising technique for evaluating the diaphragm during mechanical ventilation, where loss of diaphragm thickness over time can indicate atrophy as mentioned earlier [27].

## MATERIAL AND METHODS

**Sample:** A total of 55 patients of both genders, aged between 30 and 45 years who were admitted to Kasr El-Ainy and Fever Hospitals' intensive care units and tested positive for COVID-19 between June 2020 and March 2021 were included once they had been intubated and mechanically ventilated due to acute respiratory failure based on arterial blood gases [pH, $PaO_2$ and $PaCO_2$].

**Randomization:** patients fit-to-criteria were randomly assigned into one of two groups [32 study and 23 control] based on the number of enrollments in the study. All patients with even enrollment numbers were assigned to the study group, while those with odd numbers were assigned to the control group.

**Evaluation procedures:** For each included patient, diaphragmatic thickness in both inspiration [$T_{insp}$] and expiration [$T_{exp}$] was measured using a 7–10 MHz linear high-frequency probe transducer for adults [14]. Assessment was conducted by the same blinded clinician in the first 24±4 hours of commencing mechanical ventilation. Diaphragmatic thickness fraction [$TF_{di}$] was then calculated based on the following equation:

$$TF_{di} = \frac{Tinsp - Texp}{Texp} \times 100$$ [26,27]

All measurements were performed with the patient in the supine or semi-recumbent position on the right side only. The probe was held perpendicular to the skin in the anterior axillary line between 7-9 intercostal spaces using the liver as a sonographic window to measure diaphragmatic thickness at the zone of apposition [ZOA] [28,29]. In this technique, the diaphragm is visualized as a three-layered structure that appears superficial to the liver, consisting of a muscular layer that is relatively non-echogenic bounded by two echogenic layers [i.e., pleura and peritoneum] [30] as illustrated in **[Figure 1]**.

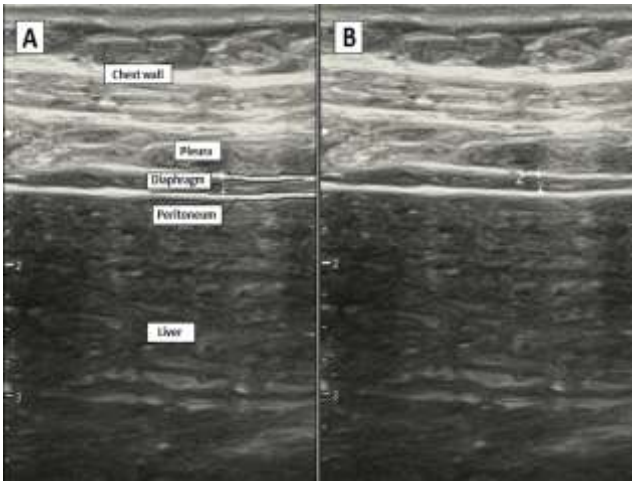


**Figure [1]:** An image of the right hemidiaphragm obtained by ultrasonography in zone of apposition with the diaphragm labeled between the pleura and peritoneum as seen from a hepatic window **[A]** The same picture of diaphragm can be identified without labels, the distance between the cross marks represents diaphragmatic thickness **[B].**

For all recorded initial measurements, the subsequent measurement was acquired after 72 hours of the initial assessment by the same blinded investigator.

**Inclusion criteria:** Patients included in this study were of both genders, aged between 30 and 45 years, with BMI ≤ 35 kg/m$^2$, tested positive for COVID-19 based on PCR and were mechanically ventilated due to type [I] respiratory failure based on ABGs [$PaO_2$<60mmHg] within 1-2 day of ICU admission. All included patients were Intubated via endotracheal tubes, mechanically ventilated using a mode that completely or partially unloads the diaphragm. [i.e., CMV, AC or PS] with likelihood of continuing mechanical ventilation for at least 72 hours. Inclusion data and vital

signs of patients were recorded and traced to make sure patients included in both groups are not significantly different in terms of disease severity and hemodynamic status.

**Exclusion criteria:** Patients with the conditions stated in [Table 1] were excluded from the study at the start, and for included patients who developed at least one of these conditions during the study, IMT was discontinued and they were also excluded.

**Table [1]:** Criteria of patients who were excluded from the study

| Condition | Examples | Explanation |
|---|---|---|
| Conditions that affect the diaphragm | - NMD* with progressive muscle wasting.<br>- Known anatomical malformation of the diaphragm.<br>- Phrenic nerve palsy.<br>- COPD* with emphysema and a flat diaphragm.<br>- Neurological conditions that affect central control of respiration.<br>-Type II and mixed respiratory failure. | The pathology of these conditions affects diaphragmatic thickness by either atrophy, or pseudohypertrophy due to the increased load on the inspiratory muscle. |
| Conditions that affect ultrasonic visualization of the diaphragm | - Pleural disease.<br>- Hepatic problems. | Unclear US* visualization of the diaphragm in the ZOA* that may lead to false measurements |
| Ventilation parameters that do not completely unload the diaphragm | - NIV*<br>Spontaneous modes of ventilation. [e.g., CPAP*, BiPAP*] | These modes do not fully unload the diaphragm. |
| History of MV* in the past 4 months prior to this inclusion | | There might be pre-existing change in diaphragmatic thickness due to previous MV |

*NMD: Neuromuscular diseases; COPD: Chronic obstructive pulmonary disease; US: Ultrasonographic; ZOA: Zone of apposition; NIV: Non-invasive ventilation; CPAP: Continuous positive airway pressure; BiPAP: Bilevel positive airway pressure; MV: Mechanical ventilation.
NB: This table only includes conditions that we excluded prior to or during this study for the sake of study accuracy and specificity. However, they are not known to be contraindicated for IMT and thus specific pathologies must be studied separately.

**Sedation Regiment:** Upon MV, patients of both groups were sedated using a combination of Fentanyl [0.6 to 3.6µg/kg/h] and Dormicum [Midazolam] [0.015 to 0.09 mg/kg/h] by continuous IV infusion [31]. The exact dose for each patient was calculated and titrated as per the intensivist or anaesthesiologist in charge.

## Intervention Procedures

### *Pre-training Preparation*

Before training was started, cardiorespiratory variables [respiratory rate, heart rate, systolic and diastolic blood pressures, and oxyhaemoglobin saturation] were noted to ensure that the patient is stable and not contraindicated for the training.

The ventilator alarms were checked– if any– and sources of external disturbance [e.g., retained secretions, circuit occlusions or leakage] were eliminated to ensure proper visualization of ventilator's graphs as an efficient method to monitor patient-ventilator interactions as these factors can interfere with the waveforms and can lead to misinterpretation or missed information. The pressure of the endotracheal tube cuff was maintained at 30 mmHg during the training session to make sure no leakage is compromising patients' inspiratory effort.

## Core of the training

### *Determining Initial Intensity*

On the first day of mechanical ventilation, MIP was recorded by performing an expiratory hold of 20-30 seconds and recording the greatest inspiratory pressure a patient can generate against a closed circuit 3 times and then calculating average MIP. This final measurement was used to determine the initial trigger sensitivity at which the training commenced. All patients who could perform MIP manoeuvre on the first day of mechanical ventilation were trained at 20% of their initial average MIP. Patients who were sedated or unable to voluntarily and maximally inhale against an occluded circuit underwent triggering trials to determine the highest tolerated trigger sensitivity. In these trials, the triggering pressure was increased by 5 $cmH_2O$ starting at the sensitivity previously set by the intensive care physician. At every new sensitivity, the patient was observed for signs of distress, and the ventilator graphs were observed for signs of ineffective effort. The trigger sensitivity was thus increased by additional 5 $cmH_2O$ if 6 successive patient-triggered breaths were completed with no signs of distress or asynchrony. When the trigger threshold at which patient failed to trigger at least 6 complete breaths was reached, the trial is terminated and training was started at the last tolerated triggering pressure.

### *Training Progression*

After determining the initial triggering threshold, patients were set to a pressure support mode with the pre-determined trigger sensitivity set, and the patient was observed while breathing against the new triggering sensitivity. The first session was performed on the first day of mechanical ventilation, consisted of 10 breaths x 3 sets followed by 30 seconds of rest and repeated throughout the duration of the session. Initially, the first session lasted for 5 minutes of active training time, and additional 5 minutes were added to every following session with the resting time

excluded using a stop-watch. When the patient could successfully tolerate 30 minutes of training, a new trigger sensitivity was obtained as previously explained and the training protocol was repeated for the 72 hrs following MV. During the training, two therapists or a therapist and a nurse closely monitored the patients' vital signs and patterns of breathing along with the ventilator graphs. It was normal for a patient to show signs of inspiratory delay but not ineffective effort with higher values of triggering thresholds; Repeated detection of wasted or ineffective effort required revision of the initial triggering threshold.

There were no fixed hours at which the training sessions were performed because patients had different medication, feeding and turning schedules, in addition to the medical interventions that took place at unpredictable hours. However, sessions were repeated 3-5 times/day with a 2-hour-gap between sessions.

### *Session Termination Protocol*

Sessions were terminated immediately if one of the termination criteria in [Table 2] were detected during the session. The following session was resumed normally if the terminating event has already subsided. Typically, therapists provided 5 sessions/day, however, due to the unpredictable events in critical care settings, patients who had one or two sessions terminated/day were kept included in the study, while those who could not tolerate or did not complete at least 3 sessions/day were permanently excluded from the study.

### *Finalizing the Training*

After the session duration was completed, patients' initial ventilatory settings were restored according to the attending physician, all vital signs were recorded again one minute after the end of the protocol. All patients were followed up for the study duration [72 hours], unless they were weaned, titrated to spontaneous breathing modes of MV, were tracheostomized or developed one or more of the exclusion criteria in [Table 1].

### Statistical analysis

Between-groups, comparison was performed by unpaired t-test for numerical data and by chi-squared test for categorical data. Shapiro-Wilk test was used to test the normal distribution of data. Levene's test for homogeneity of variances was done to examine the homogeneity between groups. Mean values of inspiratory and expiratory diaphragmatic thickness and fraction thickness between the study and control groups were tested by unpaired t-test. Paired t-test was conducted for comparison between pre and post intervention in each group. Chi squared test was conducted to investigate the correlation between severity of condition and response to IMT. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis was conducted through the statistical package for social studies [SPSS] version 25 for windows [IBM SPSS, Chicago, IL, USA].

**Table [2]:** The inspiratory muscle training protocol used in this study

| Parameter | Details |
|---|---|
| IMT method | Inspiratory muscle load was delivered by adjusting the triggering pressure-threshold of the ventilator. |
| Training initiation duration | training was initiated on the first day of mechanical ventilation following the initial assessment. The first session lasted for a duration of 5 minutes and the duration was increased by 5 minutes in every consecutive session, until the duration reached 30 minutes. Then the intensity was taken to the next level [20] |
| Frequency | 10 breaths × 3 sets, 3-5 times/day for the duration of the study [3 days].[20] |
| Intensity | The trigger sensitivity was adjusted to 20% of the first recorded maximum inspiratory pressure [MIP].[20] If MIP could not be obtained [in case of sedation or poor consciousness], trigger sensitivity was set to the highest pressure at which the patient could trigger 6 successive breaths without demonstrating signs of difficulty or distress. |
| Progression | If a patient tolerated 30 minutes of IMT, the next session was performed with increasing trigger sensitivity by 20% of the new MIP, [20,21,24] or triggering trial was repeated for unconscious patients. |
| Session Termination | an IMT session was terminated if the patient demonstrated signs of intolerance or distress including respiratory rate > 35 breaths/min during the trial, development of paradoxical breathing, SpO2 less than 85%, > 20% in heart rate compared to the baseline heart rate, systolic blood pressure more than 180 mmHg or less than 90 mmHg, diaphoresis, irritability, arrhythmia, convulsions, or sweating.[32] |

## RESULTS

Tables [3 and 4] showed patients' characteristics of the study and control groups. There was no significant difference between groups in age, sex, BMI and modes of mechanical ventilation. distribution nor in initial ABGs, vital signs, PEEP and $FiO_2$ [$p > 0.05$].

### Effect of IMT on diaphragmatic thickness:

There was a significant increase in inspiratory and expiratory diaphragmatic thickness of the study group post intervention compared with that pre-intervention [$p < 0.001$]. The percent of increase in inspiratory and expiratory diaphragmatic thickness of the study group was 14.13% and 8.65% respectively. There was no significant difference in fraction thickness of study group between pre and post intervention [$p > 0.05$]. There was a significant decrease in inspiratory and expiratory diaphragmatic thickness and fraction thickness of the control group post-intervention compared with that pre-intervention [$p < 0.001$]. In addition.

There was no significant difference between groups pre-intervention [p > 0.05]. Comparison between groups post-intervention revealed a significant increase in inspiratory and expiratory diaphragmatic thickness of the study group compared with control group [p < 0.01 [Table 5, Figure 3].

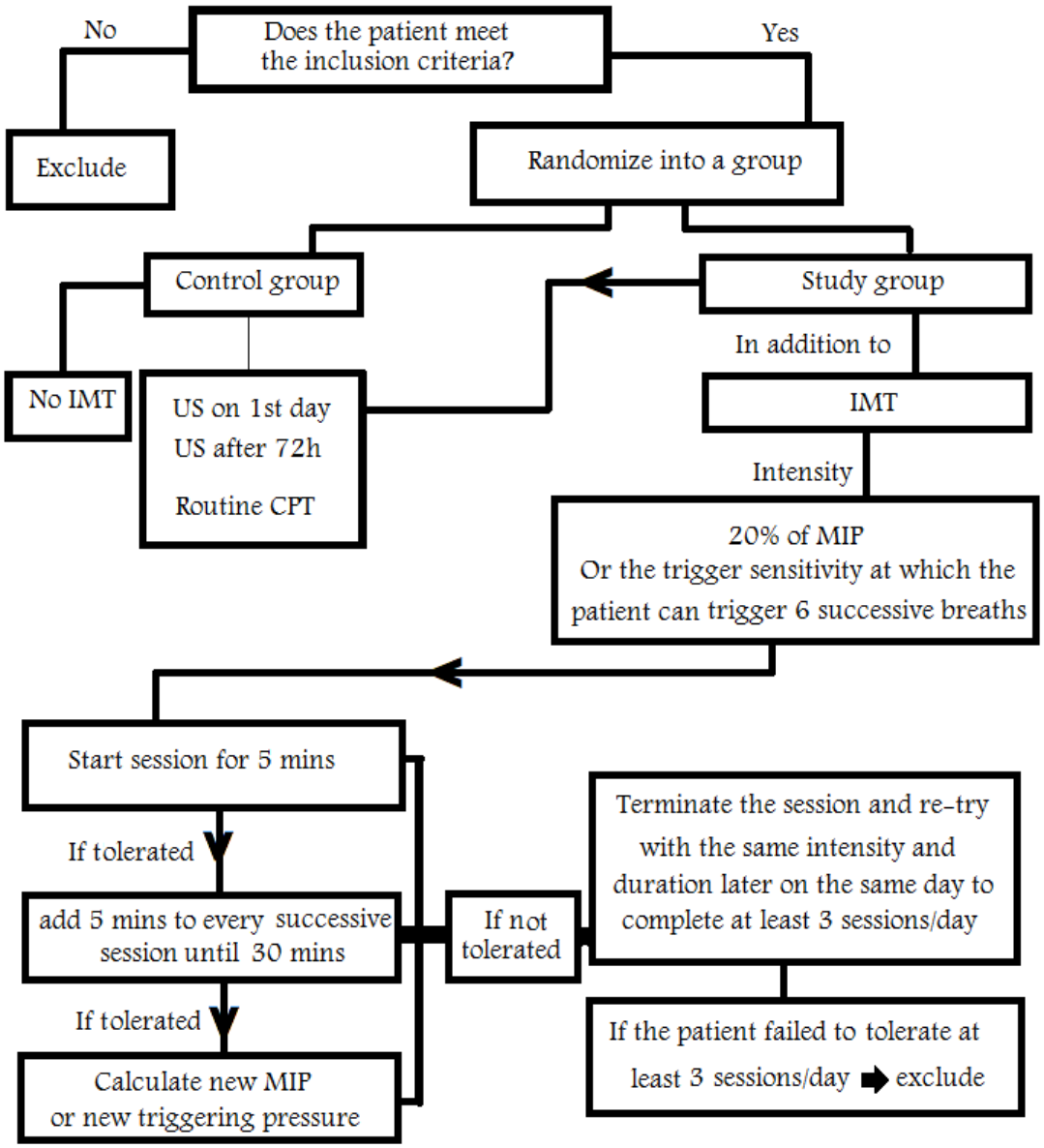


Figure [2]: Flowchart of the training protocol

**Table [3]:** Basic characteristics of participants.

| | Study group | Control group | p-value |
|---|---|---|---|
| Age, mean ± [SD*], years | 38.31 ± 4.94 | 38.13 ± 4.28 | 0.88 |
| Sex, n [%] | | | |
| Females | 14 [44%] | 9 [39%] | 0.73 |
| Males | 18 [56%] | 14 [61%] | |
| Mode of mechanical ventilation, n [%] | | | |
| CMV-AC/PC | 14 [44%] | 8 [35%] | 0.26 |
| CMV-AC/VC | 8 [25%] | 3 [13%] | |
| PS | 10 [31%] | 12 [52%] | |

***SD**: standard deviation; **p-value:** probability value; **CMV:** Controlled mandatory ventilation; **AC:** Assist Control; **PC:** Pressure Control; **VC:** Volume Control; **PS:** Pressure support.

**Table [4]:** Between-group comparison of inclusion data and vital signs throughout study duration

| Data | Day | Study | Control | *t*-score | *P* value | Significance |
|---|---|---|---|---|---|---|
| **BMI [kg/m²]** | NA | 27.2 ± 2.5 | 28.4 ± 3.03 | 1.60 | 0.114 | NS |
| **HR [beat /min]** | 1 | 115.4±9.4 | 119.7±11.6 | 1.51 | 0.135 | NS |
| | 2 | 110.2±9.2 | 112.4±7.6 | 0.93 | 0.35 | NS |
| | 3 | 108.3±4.6 | 105.8±6.9 | 1.61 | 0.112 | NS |
| **RR [c/min]** | 1 | 27.1±7.6 | 29.9±5.2 | 1.52 | 0.132 | NS |
| | 2 | 22.7±8.5 | 26.3±7.4 | 1.63 | 0.108 | NS |
| | 3 | 20.1±2.6 | 18.9±3.8 | 1.39 | 0.169 | NS |
| **pH** | 1* | 7.36±0.12 | 7.37±0.07 | 0.35 | 0.722 | NS |
| | 2 | 7.34±0.06 | 7.36±0.03 | 1.46 | 0.147 | NS |
| | 3 | 7.35±0.11 | 7.38±0.04 | 1.24 | 0.217 | NS |
| **$PaCO_2$ [mmHg]** | 1* | 37.2±8.5 | 36.5±9.1 | 0.29 | 0.77 | NS |
| | 2 | 47.5±4.2 | 42.8±8.7 | 2.60 | 0.011 | S |
| | 3 | 44.8±8.7 | 41.3±6.9 | 1.6 | 0.11 | NS |
| **$PaO_2$ [mmHg]** | 1* | 51.8±6.4 | 54.6±8.3 | 1.41 | 0.16 | NS |
| | 2 | 97.5±14.8 | 94.6±11.6 | 0.78 | 0.43 | NS |
| | 3 | 91.6±9.5 | 95.7±5.5 | 1.58 | 0.06 | NS |
| Mean MV settings for the complete study duration | | | | | | |
| **$FiO_2$ [%]** | | 55.75±10.15 | 57.6±13.13 | 0.60 | 0.54 | NS |
| **PEEP [mmHg]** | | 10.8±2.2 | 10.4±2.1 | 0.67 | 0.5 | NS |

[1*]: represents the last ABG recording before commencing mechanical ventilation.

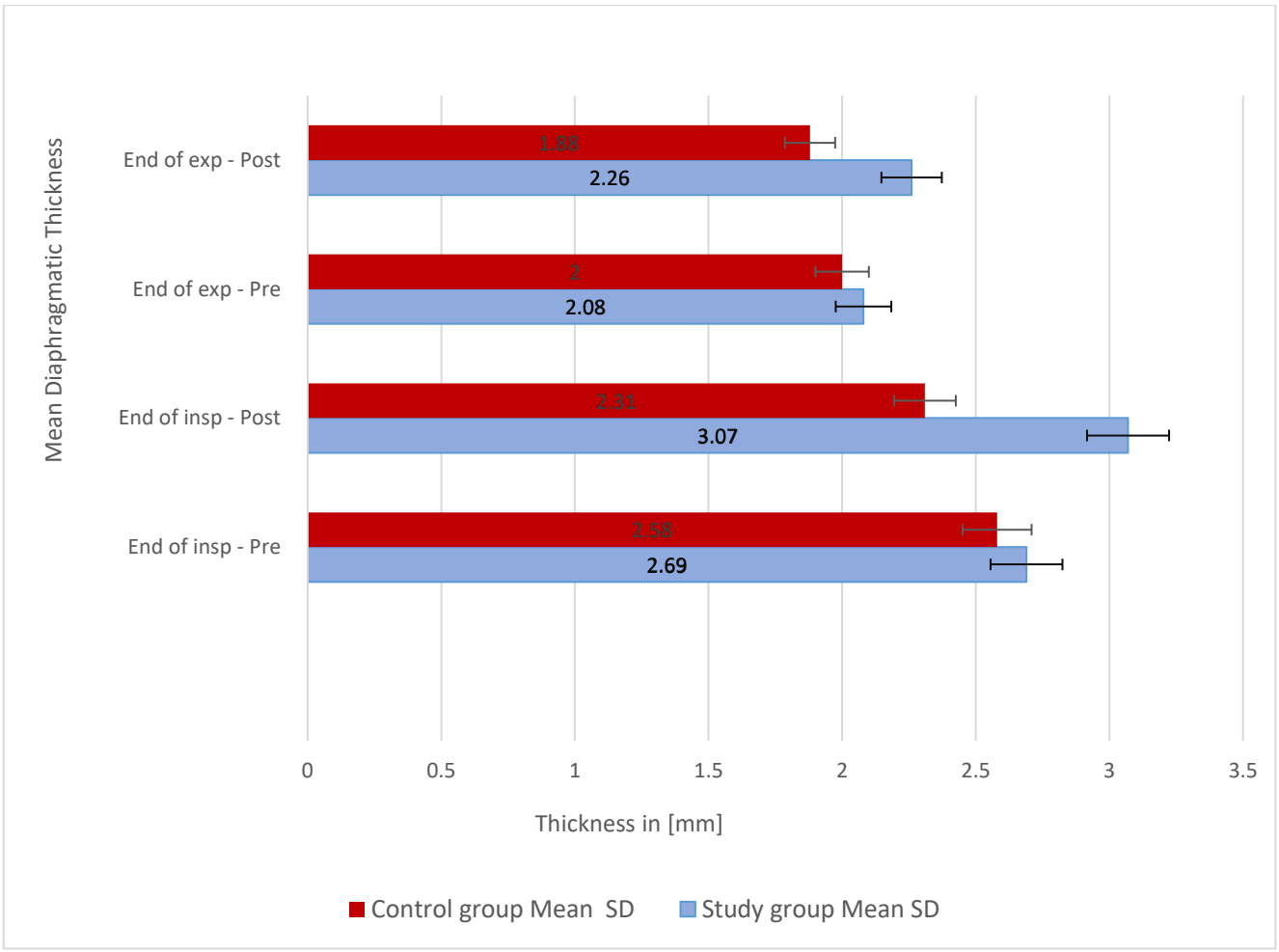


Figure [3]: Changes in pre and post mean diaphragmatic thickness in both groups

Table [5]: Between-group comparison of mean diaphragmatic parameters pre and post intervention

| Thickness at the end of inspiration [mm] | **Study group** | **Control group** | **MD [95% CI]** | **t- value** | **p value** |
|---|---|---|---|---|---|
| | Mean ± SD | Mean± SD | | | |
| Pre | 2.69 ± 0.27 | 2.58 ± 0.48 | 0.11 [-0.9:0.31] | 1.07 | 0.28 |
| Post | 3.07 ± 0.37 | 2.31 ± 0.46 | 0.76 [0.53:0.99] | 6.75 | 0.001 |
| **MD [95% CI]** | -0.38 [-0.5: -0.25] | 0.27 [0.21:0.32] | | | |
| **% of change** | 14.13 | 10.47 | | | |
| ***t*- value** | -6.39 | 10.5 | | | |
| | *p = 0.001* | *p = 0.001* | | | |
| Thickness at the end of expiration [mm] | | | | | |
| Pre | 2.08 ± 0.3 | 2 ± 0.43 | 0.08 [-1.02:0.29] | 0.97 | 0.33 |
| Post | 2.26 ± 0.36 | 1.88 ± 0.43 | 0.38 [0.16:0.59] | 3.55 | 0.001 |
| **MD [95% CI]** | -0.18 [-0.23: -0.13] | 0.12 [0.06:0.14] | | | |
| **% of change** | 8.65 | 6 | | | |
| ***t*- value** | -7.31 | 4.89 | | | |
| | *p = 0.001* | *p = 0.001* | | | |
| Thickness fraction [%] | | | | | |
| Pre | 30.56 ± 14.82 | 30.58 ± 7.18 | -0.02 [-6.74:6.68] | -0.008 | 0.99 |
| Post | 32.87 ± 16.85 | 23.13 ± 7.27 | 9.74 [2.22:17.26] | 2.59 | 0.006 |
| **MD [95% CI]** | -2.31 [-5.51:0.89] | 7.45 [5.02:9.89] | | | |
| **% of change** | 7.56 | 24.36 | | | |
| ***t*- value** | -1.47 | 6.35 | | | |
| | *p = 0.15* | *p = 0.001* | | | |

**SD:** standard deviation; **MD:** mean difference; **CI:** confidence interval**; p-value:** probability value.

## DISCUSSION

The results of this study support the literature's previous reports that patients receiving mechanical ventilation begin to develop diaphragm thinning soon after intubation resulting in complications, delayed weaning and high risk of mortality [11,21,33]. This is why the attempts to prevent or reverse diaphragmatic atrophy has become more important than ever.

In critical care settings, lack of patient cooperation due to sedation or disturbed conscious level is one of the obstacles that critical care therapists face while attempting to commence an early rehabilitation programme [6,34]. The IMT protocol proposed in this study focused on requiring only minimal or no patient cooperation. Thereby, it can be used in sedated, unconscious patients without the need for active participation. Several studies in literature have reported the effectiveness of IMT in mechanically ventilated patients throughout the past decade. However, the majority of these studies used threshold external devices to load the diaphragm by connecting an adaptor threshold device to the patients'' endotracheal or tracheostomy tubes [20, 21, 35,36].

Adjusting the ventilator's trigger sensitivity was also reported as an easy method that can be started on the first day of mechanical ventilation [24]. In this study, this method was preferred because it does not need any additional or special equipment other than the ventilator itself. It also requires minimal circuit disconnection and allows for proper oxygenation and thorough monitoring of patients' respiratory parameters as they breathe against load. In addition, it was safe to use in recruited lungs of COVID-19 patients with respiratory distress, and it allowed customized adjustment of the load based on each patient's individual respiratory effort.

It is evident that loss of diaphragmatic thickness is associated with reduced respiratory effort and tidal volume as well as poor prognosis and weaning outcomes [12,21,33]. Yet, because weaning is a multi-factorial process, it is difficult to tell whether inspiratory muscle training directly contributes to better weaning outcomes [12]. Therefore, this study focused on studying the direct effect of the proposed IMT protocol on diaphragmatic thickness. Interestingly, this protocol not only could prevent diaphragmatic thinning in all study group patients, but also could increase diaphragmatic thickness in 53% of them.

In order to discuss the reported changes in diaphragmatic thickness, the findings are divided into: a] diaphragmatic thickness at the end of inspiration [$T_{di\text{-}insp}$], b] diaphragmatic thickness at the end of expiration [$T_{di\text{-}exp}$] and c] thickening fraction of the diaphragm [$TF_{di}$].

**Diaphragmatic thickness at end of inspiration:** When the diaphragm contracts during inspiration, its fibers shorten, and complete absence of this thickening during

inspiration is diagnostic for diaphragmatic paralysis. When the muscle atrophies, thickness decreases and the diaphragm does not show proper contraction during inspiration [25].

In this study, the control group's mean diaphragmatic thickness at the end of inspiration decreased by 10.47% after 72 hours compared to the first day of mechanical ventilation. Which supports previous studies that the diaphragm undergoes a series of atrophying events soon after intubation and mechanical ventilation [11,12,21,37,38]. In contrast, there was a 14% increase in mean diaphragmatic thickness at the end of inspiration in the study group that received inspiratory muscle training as a part of an early rehabilitation programme. Which suggests effectiveness of this protocol in preserving inspiratory diaphragmatic thickness.

It is worth mentioning that this study was limited by absence of other measurements that could confirm whether this increase in inspiratory thickness reflects real increase in respiratory effort [e.g., MIP or transdiaphragmatic pressure]. It is possible that the witnessed increase in inspiratory thickness may be due to injurious changes in the diaphragm. In other words, it may be the result of excessive inspiratory loads during ventilation or from systemic inflammation [11,39].

High inspiratory loads due to inadequate ventilator settings –or even IMT– might have caused myofibrillar and sarcolemmal injury. In addition to the changes in myofibrillar structures, tissue oedema or tonic diaphragm activity might cause similar changes in diaphragmatic thickness [11].

**Thickness at end of expiration:** Diaphragmatic thickness at the end of expiration [$T_{di\ exp}$] is an indicator of diaphragmatic atrophy rather than weakness; its decrease is associated with lower inspiratory effort and a higher risk for complications and weaning difficulty [40].

In previous studies, it was reported that diaphragmatic thickness at end of expiration decreased by 6-7.5% per day on MV and there was a linear relationship between the incidence of diaphragmatic atrophy and the level of ventilator support [5,8,12]. The current study supports these reports by revealing that patients who did not receive inspiratory muscle training showed a mean of 6% decrease in diaphragmatic thickness at the end of expiration. While those who received IMT showed a mean of 8.6% increase in their $T_{di\text{-}exp}$ by the third day of training, which indicates the effectiveness of this protocol in preventing diaphragmatic thinning. Speaking of limitations, the amount of PEEP – which may affect diaphragmatic thickness in expiration – was not considered during ultrasonographic assessment in this study.

**Diaphragmatic thickness fraction**

**Goligher *et al***. [11,37] reported that "diaphragm thickness was increased in some subjects and decreased in others, but both groups had significant diaphragm dysfunction when evaluated by thickening fraction." For this reason, they referred to the diaphragm thickening fraction as a more reliable indicator of diaphragmatic function than diaphragm thinning.[12] similar to thickness at the end of expiration, a decrease in thickness fraction is associated with lower inspiratory effort levels while its increase is associated with higher inspiratory effort levels. This draws a conclusion that some intermediate level of loading may be optimal [40].

In our findings, diaphragmatic thickness fraction significantly decreased by a mean of 24% in control patients who were mechanically ventilated and did not receive inspiratory muscle loading which is the same finding as many of the previous researches [8,11,41,42].

In the study group, the mean of thickening fraction on the first day of mechanical ventilation was 30.56 ± 14.82%, after 3 days of mechanical ventilation and the receipt of inspiratory muscle training 3-5 times daily the mean of thickening fraction values was 32.87 ± 16.85% with a mean of 7.5% increase in diaphragmatic thickness fraction which was reported as statistically insignificant. However, this minimal increase indicates successfully preserving inspiratory effort in these patients.

**Limitations and recommendations**

Although the inclusion criteria were unified for all patients in order to obtain a reliable sample, there are some variations [e.g., level of previous physical activity, pre-existing comorbidity…etc.] that were not taken into consideration. In addition, some circumstances and events that may have occurred during the study could not be modified nor controlled, and could potentially affect the results of the study [e.g., changes and differences in pharmacological treatments, sedation and nutrition protocols, iatrogenic complications, episodes of hemo-dynamic instability and the progression of the pathology]. Moreover, despite the fact that females were reported to have thinner diaphragms than males, both genders were equally included in the current study because each patient was compared to their initial measurements and then the between-group comparison was conducted using the percentage of change in both groups. Thus, influence of the physiological difference in diaphragmatic thickness between males and females was overruled. However, it is important for future researches to further investigate whether response to IMT varies between different genders. Not to mention that adjusting the ventilator's trigger sensitivity

briefly loads the diaphragm at the point of breath initiation; the resistance imposed by the ventilator's valve does not persist during the complete breathing cycle. Although the training duration was increased to 30 minutes, there is still lack of correlation between the effect of IMT on diaphragm endurance in need to be highlighted in future research.

## Conclusion

Inspiratory muscle training by adjusting the ventilator's trigger sensitivity using the training parameters mentioned in this study is effective in preventing diaphragmatic atrophy in mechanically ventilated patients with hypoxic respiratory failure due to COVID-19, it can safely be started as early as on the first day of mechanical ventilation regardless patients' level of consciousness. However, this protocol occasionally led to an increase in diaphragmatic thickness. Thereby, further studies are required to investigate whether this occasional increase in thickness is related to actual increase in diaphragmatic strength and endurance.

## Conflict of interest

On behalf of all authors, the corresponding author reports no conflict of interest in this work.

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