RESEARCH ARTICLE

Diaphragm muscle thinning in mechanically ventilated critically ill patients

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Abstract

Objective: The aim of this study was to investigate the course of diaphragm changes in mechanically ventilated patients in ICU after four days of mechanical ventilation. In addition, to evaluate correlation of various demographic variables to baseline diaphragm muscle thickness and their effects on the course of diaphragm muscle thickness changes.

Methods: This study was conducted from December 2018 to February 2019 at Cipto Mangunkusumo National Hospital. Thirty critically ill patients using mechanical ventilation in the ICU were included. Baseline demographic data were collected. Baseline end expiratory diaphragm thickness was measured within one hour after starting mechanical ventilation and repeated every 24 hours for four days. Mortality and duration of mechanical ventilation were recorded.

Results: There were no differences in baseline diaphragm thickness according to gender, body mass index and modified Rankin Score. The subjects were divided into two categories: duration of mechanical ventilation less than seven days and duration of ventilation of seven days or more. The mean baseline diaphragm thickness was 2.11 + 0.15 mm. A rapid decrease of diaphragm muscle thickness was found within 24 hours. Diaphragm muscle thickness changed over subsequent measurements during observation. It was found that rapid diaphragm muscle thinning corresponded with longer duration of mechanical ventilation and worse outcomes.

Conclusion: Diaphragm muscle thinning was seen early in the course of mechanical ventilation. Diaphragm muscle thickness changed over time, and there was no correlation with other measured variables.

Keywords: Diaphragm muscle thickness, Mechanical ventilation. (JPMA 71: S-78 [Suppl. 2]; 2021)

Introduction

One of the most frequent interventions in the intensive care unit (ICU) is mechanical ventilation. Epidemiological studies have shown that the trend of using either invasive or non-invasive mechanical ventilation is increasing.[1,2] Using mechanical ventilation is not without risks. It increases the risk of ventilator-associated pneumonia, haemodynamic derangement, barotrauma, volutrauma and atelectrauma. Recently, Goligher et al., reported that mechanical ventilation also caused myotrauma.[1]

The diaphragm is considered the main muscle of respiration. The function of diaphragm is one of the critical determinants of ability of the patient to be weaned off and disconnected from mechanical ventilation. At some point during their ICU care, up to 80% of patients had some respiratory muscle weakness with different severity and duration.[2] Therefore, the ability to assess diaphragm muscle thickness and function on a regular basis is important in daily intensive care practice. Early detection of diaphragm dysfunction and early intervention could reduce the duration of mechanical ventilation and prevent adverse effects.

Various modalities have been used to evaluate diaphragm function, including computed tomography scanning, magnetic resonance imaging, trans-diaphragmatic pressure monitoring and, more recently, ultrasound. Compared to other modalities, ultrasound has several advantages. It is readily used at the bedside, non-invasive, free of radiation exposure and relatively easy to learn.

Although ultrasound imaging is said to be operator dependent, Schepens et al., found that the coefficient of reproducibility of measuring diaphragm muscle thickness by ultrasound was high at 0.97 for inter-observer variability and 0.95 for intra-observer variability.[3] In a prospective study, Dhungana et al., found a similarly high intra-observer variability of 0.99 and inter-observer variability of 0.99.[4]

Holtzhausen showed in his research that diaphragm muscle thickness measured by ultrasound and diaphragm strength were moderately correlated.[5] Schepens et al., found that median time to the nadir of diaphragm muscle thinning was three days, and diaphragm muscle thickness changes after 72 hours did not correlate with the time

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spent on ventilators afterwards.[3]

The aim of this study was to investigate the course of diaphragm changes in mechanically ventilated patients in ICU after four days of mechanical ventilation. In addition, to evaluate correlation of various demographic variables to baseline diaphragm muscle thickness and their effects on the course of diaphragm muscle thickness changes.

Patients and Methods

This prospective observational study was designed to understand the course of diaphragm muscle thinning in mechanically ventilated critically ill patients at Cipto Mangunkusumo National Hospital. Approval was obtained from Ethics Committee of Universitas Indonesia (1020/UN2.F1/ETIK/2018), and the study was recorded in ClinicalTrials.gov (NCT03933332).

Between December 2018 and February 2019, all newly admitted patients to ICU were evaluated for potential recruitment for the study. After obtaining informed consent from patients or their legal guardians, adult patients who had been newly started on mechanical ventilation with a modified Rankin Score at least below 4 within one month before admission to ICU were included. The exclusion criteria were: 1. pregnant women; 2. intubation for more than 24 hours before ICU admission; 3. cardiac or chest surgery patients; and 4. patients with peripheral musculoskeletal diseases. It was estimated from previous research that 27 subjects were needed for this study; therefore, assuming a 10% dropout rate, the total number of subjects needed was 30.

Each patient's baseline demographic data were collected and their diaphragm muscle thickness was measured within one hour after admission to ICU. Subsequent diaphragm muscle thickness measurements were conducted every 24 hours time frame after previous measurement until there were five measurements for each patient. Further diaphragm muscle thickness was not measured beyond fifth day in accordance with Schepens et al., findings that the nadir of diaphragm muscle thinning was found at 72 hours after starting mechanical ventilation.[3]

Before measurement, subjects were placed in supine position at bed inclination. Diaphragm muscle thickness was measured at the zone of apposition on mid-axillary line in eighth or ninth right intercostal space using Grosu's standardised technique.[6] The probe orientation had to be adjusted until the diaphragm was properly visualised. The diaphragm was identified as a less echogenic muscle structure between the parallel lines of pleural and peritoneal membranes. Diaphragm muscle thickness was measured at the end of expiration period. Three measurements of diaphragm muscle thickness were taken, and the mean of those three measurements was calculated. A skin marker was used to mark the location of first probe placement to ensure that operator placed the probe in same place for follow-up measurements.

To minimize measurement bias, all measurements were conducted by one certified radiologist using a Samsung SonoAce R3 (Korea) ultrasound machine with a 10-15 MHz high frequency linear transducer. All diaphragm ultrasound images were then stored in a Picture Archiving and Communication System for further evaluation. All subjects were followed up until discontinuation of mechanical ventilation and discharge from the ICU. The duration of mechanical ventilation, length of ICU stay and mortality were reported as outcome measurements.

Statistical analysis was performed with STATA/IC 15.1 for Mac (StataCorp, College Station, TX, USA). All data collected were reported as mean ± standard deviation (SD) or median [interquartile range (IQR)]. Changes in diaphragm muscle thickness were calculated as ratios to the baseline diaphragm muscle thickness measurement. The relationship between subjects' characteristics and diaphragm muscle thickness were tested using t-test for independent groups for continuous variables and Chi-square or Fisher exact tests for categorical variables. All subjects were categorised into two groups according to length of ventilator use. Group A included subjects who used ventilator for less than seven days, and Group B included subjects who used ventilator for at least seven days. In this paper, analysis was focused on evaluating course of diaphragm muscle thinning in mechanically ventilated critically ill patients. A repeated measure ANOVA was conducted to identify differences in ratios of diaphragm muscle changes within measurements and between groups.

Results

This is the first ultrasound study of diaphragm muscle thickness in the zone of apposition conducted in critically ill patients in Indonesia. The plan was to enroll 52 patients for the study; seven patients were excluded because they did not give consent to be included, and fifteen patients did not complete follow-up measurements due to deteriorating conditions or death. Ultimately, there were only thirty patients who had five measurements of diaphragm muscle thickness. Twelve patients were on mechanical ventilation for less than seven days, while duration of mechanical ventilation was seven days or

Table-1: Baseline demographic data of subject characteristics in relation to duration of mechanical ventilation.

Variable	Total (n = 30)	Duration of ventilation less than seven days (n =12)	Duration of ventilation seven days or more (n = 18)	p
Sex				
- Male	12 (40.00%)	4	8	0.41[a]
- Female	18 (60.00%)	8	10	
Mean age (years)	48.9 ± 2.84	48.00 ± 4.51	49.50 ± 3.75	0.80[b]
Mean Height (cm)	161.27 ± 1.17	160.33 ± 1.52	161.89 ± 1.69	0.74[b]
Mean Body weight (kg)	59.06 ± 2.04	56.67 ± 2.64	60.07 ± 3.26	0.83[b]
Mean body mass index (kg/m^2)	22.64 ± 0.68	22.06 ± 3.16	23.03 ± 4.09	0.49[b]
SOFA Score				
- 0 to 6	19 (63.33%)	9	10	0.58[a]
- 7 to 9	6 (20.00%)	2	4	
- 10 to 14	5 (16.67%)	1	4	
- More than 15	0	0	0	
Mean tidal volume per body weight (ml/kgBW)	7.72 ± 0.36	7.94 ± 0.43	7.58 ± 0.53	0.62[b]
Mean Maximum pressure (mmHg)	15.83 ± 0.52	16.00 ± 0.85	15.72 ± 0.67	0.79[b]
Mean Positive end- expiratory pressure (mmHg)	5.23 ± 0.14	5.33 ± 0.26	5.17 ± 0.17	0.57[b]
Mean Oxygen fraction (%)	41.5 ± 0.64	42.5 ± 1.31	40.83 ± 0.61	0.21[b]
Mode of mechanical ventilation on day 1				
- Controlled	1 (3.33%)	0	1	0.77[a]
- Synchronised	25 (83.33%)	11	14	
- Pressure support	4 (13.33%)	1	3	
Diaphragm muscle thinning				
- Yes	15 (50.00%)	6	9	0.65[a]
- No	15 (50.00%)	6	9	

Legend: [a]: Fisher exact test. [b]: t-test. *: Statistically significant.
SOFA: Sequential Organ Failure Assessment.

longer for remaining eighteen patients.

Table-1 shows that there were no differences in various demographic variables between the group of patients that used ventilator for less than seven days and the group that underwent mechanical ventilation for seven days or more. Also, there were no differences in initial ventilator settings between groups. After all patients had completed five diaphragm muscle thickness measurements, there were 15 subjects who had declined diaphragm muscle thickness on last measurement compared to baseline diaphragm muscle thickness. Fifteen patients had increased diaphragm muscle thickness on last measurement compared to baseline diaphragm muscle thickness.

The subgroup analysis focused on patients who had diaphragm muscle thinning on final measurement. Table-2 and Table-3 show the subgroup analysis of diaphragm muscle thinning based on diaphragm muscle thickness and diaphragm muscle thickness ratio on last observation. The mean baseline diaphragm muscle thickness in patients who had diaphragm muscle thinning was 2.11 ± 0.15 mm. Male patients had slightly thicker diaphragms of 2.35 ± 0.28 mm compared to female average of 1.99 ± 0.17 mm. However, this difference was not statistically significant.

The diaphragm muscle thickness ratio was calculated as the ratio of diaphragm muscle thickness of concern to baseline diaphragm muscle thickness. A diaphragm muscle thickness ratio below 1 meant diaphragm muscle thickness of concern was lower than baseline diaphragm muscle thickness, which indicated diaphragm muscle thinning. Diaphragm muscle thinning was more pronounced in Group B than in Group A, although the difference did not achieve level of statistical significance. In Group A, there was a 20% decline in diaphragm muscle thickness in four days, which corresponds to a rate of diaphragm muscle thinning of 4.99% per day. In group B, there was a 31% decline in diaphragm muscle thickness, which corresponds to a rate of diaphragm muscle thinning of 7.71% per day.

A repeated measures ANOVA was performed to analyse changes in ratio of diaphragm muscle thickness between subjects and within subjects in Group A and Group B. The ANOVA results indicated that there was a significant

Table-2: The course of diaphragm muscle thinning based on diaphragm thickness change ratio on last observation.

Variable	Duration of ventilation less than seven days (n =6)	Duration of ventilation seven days or more (n = 9)	P
Mean Baseline diaphragm muscle thickness (mm)	2.02 ± 0.23	2.17 ± 0.21	0.64[b]
Mean Diaphragm muscle thickness (mm) after 24 hours	2.03 ± 0.22	1.80 ± 0.19[e]	0.45[b]
Mean Diaphragm muscle thickness (mm) after 48 hour	1.99 ± 0.18	1.83 ± 0.15[e]	0.54[b]
Mean Diaphragm muscle thickness (mm) after 72 hour	1.72 ± 0.21[c]	1.67 ± 0.14[e]	0.85[b]
Mean Diaphragm muscle thickness (mm) after 96 hour	1.60 ± 0.19[d]	1.46 ± 0.13[f]	0.52[b]
Mean Duration of mechanical ventilation	4.83 ± 0.40	13.33 ± 2.09	0.04[b]
Mean Rate of decline (%/day)	4.99 ± 0.01	7.71 ± 0.01	0.27[b]
Mortality	0	4	0.09[a]

Legend: [a]: Fisher exact test; [b]: paired t-test; [c]: repeated measures ANOVA; [d]: repeated measures ANOVA: significant differences compared to baseline, 24 and 48 hours with $p < 0.05$; [e]: repeated measures ANOVA: significant differences compared to baseline with $p < 0.05$; [f]: repeated measures ANOVA: significant differences with baseline, 24, 48 and 72 hours with $p < 0.05$.

Table-3: Diaphragm muscle thickness ratio changes over measurement.

Variable	Duration of ventilation less than seven days (n =6)	Duration of ventilation seven days or more (n = 9)	P
Baseline	1.00	1.00	-
Mean Diaphragm changes in first interval time frame	1.02 ± 0.06	0.84 ± 0.06	0.07[a]
Mean Diaphragm changes in second interval time frame	1.01 ± 0.07	0.86 ± 0.05	0.11[a]
Mean Diaphragm changes in third interval time frame	0.85 ± 0.04[b]	0.79 ± 0.06	0.46[a]
Mean Diaphragm changes in fourth interval time frame	0.80 ± 0.05[c]	0.69 ± 0.05[d]	0.19[a]

Legend: [a]: paired t-test; [b]: repeated measures ANOVA: significant differences compared with first time interval with $p < 0.05$; [c]: repeated measures ANOVA: significant differences compared with first, second and third time interval with $p < 0.05$; [d]: repeated measures ANOVA: significant differences compared with all time intervals with $p < 0.05$.

effect on ratio of diaphragm muscle thickness changes within subjects with Wilks' lambda = 0.21 F (4,10) = 9.50, p = 0.02. Within subjects, there were significant differences in diaphragm muscle thickness changes from interval 3 and 4 to interval 1 and 2. Although there were differences between groups, the differences did not achieve level of statistical significance. In outcome statistics with regards to diaphragm muscle thinning, four patients died in group B, but no mortality was seen in group A. There were also significant differences in duration of mechanical ventilation. Group A had a mean duration of mechanical ventilation of 4.83 ± 0.40 days, whereas group B had a mean duration of ventilation of 13.33 ± 2.09 days.

Discussion

Our results confirm that diaphragm muscle thinning in mechanically ventilated critically ill patients, which has lately become more recognized as diaphragm dysfunction, may influence patient outcomes. Until recently, no published data on normal range of diaphragm muscle thickness among critically ill Indonesian population were available. Therefore, this is the first study as per authors' knowledge reporting on mean baseline diaphragm muscle thickness in Indonesia. Serial measurements of diaphragm muscle thickness were conducted. Therefore, evolution of diaphragm muscle thinning during mechanical ventilation in critically ill patients could be evaluated. The baseline diaphragm muscle thickness in this group with muscle thinning was 2.11±0.15 mm. This baseline diaphragm muscle thickness was comparable to baseline diaphragm muscle thickness from a previous study, which was 1.9±0.04 mm.[3]

In this study, baseline diaphragm muscle thickness was not correlated to sex, age, body mass index, baseline Sequential Organ Failure Assessment (SOFA) score or premorbid functioning. These findings are consistent with other studies, such as a study by Goligher et al., which found that baseline diaphragm muscle thickness was not influenced by baseline SOFA score, sepsis or positive end-expiratory pressure.[7] Schepens also found no correlation between baseline diaphragm muscle thickness and sex, age, premorbid condition or steroid usage.[3] The association between diaphragm muscle thickness and clinical outcomes might vary over course of time and might be influenced by many factors that were not investigated in this study. There were patients with diaphragm muscle thinning in both groups.

In subgroup analysis, focusing on diaphragm muscle thinning, this study demonstrated that difference between the two groups was in rate of diaphragm muscle thinning. The rate of decline was faster by 7.5% in the group that was mechanically ventilated for more than seven days compared to the group that was mechanically ventilated for less than seven days. The rate of diaphragm muscle thinning was comparable to previous studies. Schepens found rapid diaphragm muscle thinning of up to 9% after 24 hours of mechanical ventilation.[3] Grosu et al, found diaphragm muscle thinning of 6% per day.[6]

In 2015 Goligher found that the average ventilator driving pressure over the first 72 hours of starting mechanical ventilation was correlated with changes in diaphragm muscle thickness over the first week of mechanical ventilation.[8] Schepens et al, found median time to nadir was three days and mean nadir was 1.3 mm, which corresponds to 32% diaphragm muscle thinning.[3] After 72 hours on mechanical ventilation, diaphragm muscle thickness changes did not correlate with length of mechanical ventilation. In contrast to a previous study that measured diaphragms until patients were extubated or died, this study only observed patients for four days.[1,3,6] Therefore, no conclusions could be drawn on nadir diaphragm muscle thinning in the current study.

The diaphragm muscle thinning that we observed in our study may correspond to previously reported diaphragm myofiber atrophy and diaphragm muscle strength in mechanically ventilated critically ill patients.[9-12] Due to the continuous diaphragm assessment over 96 hours of starting mechanical ventilation in our study, we could measure the speed of muscle thinning in different subset of patients.

Patients with a faster rate of diaphragm muscle thinning had worse outcomes than patients who had a slower rate of decline. The duration of mechanical ventilation was significantly higher in patients with a faster rate of decline, and the mortality rate was also higher. Presumably, rapid thinning of diaphragm muscle might be related to more severe respiratory muscle weakness, which resulted in longer ventilator duration. Direct relationship between diaphragm thickness and diaphragm contractile activity, expressed as thickening fraction of diaphragm muscle, was described by Goligher in 2015.[8] We assumed that slower diaphragm muscle thinning might represent a reversible form of muscle failure that could recover as primary critical illness resolves. Several studies found that the level of ventilator support can impact diaphragm muscle thickness.[8,13] Adjusting the level of ventilator support may assist diaphragm muscle recovery and may lead to better outcome. Utilizing diaphragm-protective mechanical ventilation strategy can avoid harmful effect of both excessive and insufficient ventilator support.[14,15] Diaphragm thickness measurement on patients with mechanical ventilation can give information about the adequacy of the ventilator support and can help clinicians on adjusting the level of ventilator support to the patient.

There are several limitations to this study. First, it is a single-centre study with a small sample size. Therefore, caution should be used in applying the results to general population. Also, Cipto Mangunkusumo is a tertiary referral hospital. Therefore, the patients' diseases are more severe and complicated compared to those in other hospitals. Another limitation is that due to observational design of the study, all biases and confounders that might interfere with the results could not be eliminated. In addition, this study measured baseline diaphragm muscle thickness at the beginning of mechanical ventilation. This baseline diaphragm muscle thickness might not be representative of true baseline diaphragm muscle thickness at the onset of critical illness. The function of diaphragm is subject to diaphragm muscle thickness and diaphragm muscle strength. This study only assessed quantitative side of diaphragm function.

Conclusion

Diaphragm muscle thinning could be seen early at the start of mechanical ventilation. Diaphragm muscle thickness changes were very dynamic and could increase or decrease during observations, regardless of previous direction and magnitude of changes. In this study, there were no correlations between baseline diaphragm muscle thickness and sex, age, body mass index, baseline SOFA score or premorbid function. Diaphragm muscle thinning was found in both the groups, which used ventilator for less than seven days and group which used the ventilator for seven days or more. Rapid diaphragm muscle thinning was associated with an increase in mortality and longer duration of mechanical ventilation.

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