B I O L I F E   **R E S E A R C H   A R T I C L E**

Serial ultrasonographic evaluation of diaphragm thickness during mechanical ventilation in ICU patients

El Morsy A.A.[1], Ibrahim M.R[2], Sakr M.M.A[3]*

[1-3] *Department of Critical Care Medicine, Faculty of Medicine, Alexandria University*

Email: sakr_korish@hotmail.com

ABSTRACT

Objective: Serial ultrasonographic assessment of the effect of different modes of mechanical ventila-tion on diaphragmatic thickness and consequently its effect on weaning of mechanical ventilation, total ventilatory days, ICU stay and mortality.
Patients and methods: This study was carried out on 67 mechanically ventilated adult patients of both genders who were admitted to Critical Care Medicine Department in Alexandria main university hospital over a period from 1/4/2014 to 30\9\2014. All patients were subjected to complete medical and surgical history taking, complete physical examination and daily ultrasonographic assessment of diaphragmatic thickness.
Results: Diaphragmatic atrophy was detected in 15 patients (78.9%) of patients on CMV, 14 patients (60.9%) of patients on assisted MV in comparison to only one patient (4%) of patients on spontaneous MV (P<0.001). Patients who developed diaphragmatic atrophy had a mean total ventilatory days 7.23 ± 2.39 days, mean ICU stay 9.08 ± 2.91 days, mortality rate 16.7%, primary weaning failure rate 52% and secondary weaning failure rate 36% while Patients who did not develop diaphragmatic atrophy had a mean total ventilatory days 4.32 ± 2.44 days, mean ICU stay 7.59± 2.63 days, mortality rate 8.1%, primary weaning failure rate 5.4% and secondary weaning failure rate 5.4%. (P1 < 0.001 P2 = 0.03 P3 = 0.451 P4 <0.001   P5 <0.001 respectively).
Conclusion: Mechanical ventilation induces diaphragmatic atrophy which is significantly higher with controlled and assisted mechanical ventilation modes than spontaneous modes. Ventilator induced diaphragmatic atrophy is associated with higher rates of primary and secondary weaning failure, more ventilatory days, longer ICU stay.

Key Words: Mechanical Ventilation; Diaphragmatic atrophy; Weaning Failure

INTRODUCTION

Respiratory failure is a syndrome in which the respiratory system fails to maintain an ad-equate gas exchange at rest or during exercise resulting in hypoxemia with or without concomitant hypercapnia (1).

How to cite this article:

El Morsy A.A., Ibrahim M.R, Sakr M.M.A.(2015). Serial ultrasonographic evaluation of diaphragm thickness during mechanical ventilation in ICU patients. Biolife, 3(4), pp 922-936.

Respiratory failure is classified as type 1 respiratory failure or type 2 respiratory failure. (2) Type 1 respiratory failure is defined by a partial pressure of oxygen (PaO2) of <60mmHg with a normal or low partial pressure of carbon dioxide (PaCO2), Type 2 respiratory failure is defined by a PaO2 of <60mHg and a PaCO2 of >45mHg. Respiratory failure is also classified as acute, acute on chronic or chronic (3).

Mechanical ventilation (MV) is a method to mechanically assist or replace spontaneous breathing. MV is indicated when the patient's spontaneous ventilation is inadequate to maintain life. It is also indicated as prophylaxis for imminent collapse of other physiologic functions, or ineffective gas exchange in the lungs (4).

Common indications of MV are acute lung injury (ALI), apnea with respiratory arrest, acute severe asthma requiring intubation, chronic obstructive pulmonary disease (COPD), acute respiratory

acidosis with partial pressure of carbon dioxide (pCO2) > 50 mmHg and potential of hydrogen (PH) < 7.25, Increased work of breathing, hypoxemia with PaO2 < 55 mm Hg with fraction of inspired oxygen (FiO2) = 1.0, hypotension including shock and neurological diseases such as muscular dystrophy and amyotrophic lateral sclerosis (5).

Although MV is a life-saving intervention, but carries potential complications including pneumothorax, airway injury, alveolar damage, and ventilator-associated pneumonia (6) Other complications include decreased cardiac out-put, and oxygen toxicity. One of the primary complications that presents in mechanically ventilated patients is ALI/ARDS. ALI/ARDS are recognized as significant contributors to patient morbidity and mortality (7) Positive pressure ventilation appears to impair mucocilary motility in the airway which may lead to retention of secretions and pneumonia (8).

Studies have suggested that the ventilator is a likely cause of the decreased diaphragm force generating capacity (dFGC) seen in me-chanically ventilated patients. Further, mode of ventilation has been associated with dia-phragm atrophy. Animal studies suggest that even as little as 18 hours of mandatory modes of ventilation lead to diaphragm-muscle atro-phy and weakness. (9, 10)

Modes of Ventilator Support can be classi-fied to volume-targeted modes in which a fixed tidal volume is delivered with each breath and pressure-targeted modes in which the patient triggers the ventilator as in pressure support ventilation or the ventilator controls the patient's breathing as in pressure control mode (11).

Thoracic diaphragm or simply the dia-phragm is a sheet of internal skeletal muscle that extends across the bottom of the rib cage. The diaphragm separates the thoracic cavity from the abdominal cavity.(12)
The diaphragm is the principal respiratory muscle, and its dysfunction predisposes to respiratory complications and can prolong the duration of mechanical ventilation (13).

Modalities that could be used to diagnose diaphragmatic dysfunction are chest x-ray, Fluoroscopy and Sniff Test, Computed Tomography, MRI and Ultrasonography (14-21).

The use of ultrasonography has be-come increasingly popular in the everyday management of critically ill patients. It has been demonstrated to be a safe and handy bedside tool that allows rapid hemodynamic assessment and visualization of the thoracic, abdominal and major vessels structures (22).
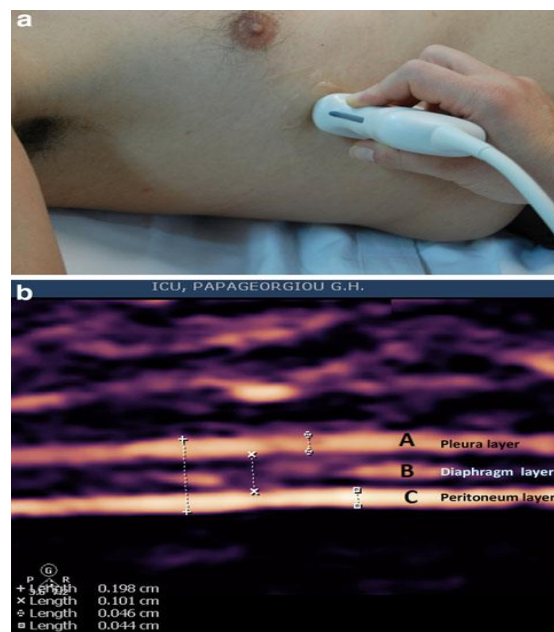
More recently-mode ultrasonography has been used in the assessment of dia-phragm kinetics. Ultrasounds provide a sim-ple, non-invasive method of quantifying dia-phragmatic movement in a variety of normal and pathological conditions (22,23).

Ultrasonography can assess the characteristics of diaphragmatic movement such as amplitude, force and velocity of con-traction, special patterns of motion and changes in diaphragmatic thickness during inspiration.(24)

These sonographic diaphragmatic pa-rameters can provide valuable information in the assessment and follow up of patients with diaphragmatic weakness or paralysis, in terms of patient–ventilator interactions during con-trolled or assisted modalities of mechanical ventilation, and can potentially help to under-stand post-operative pulmonary dysfunction or weaning failure from mechanical ventila-tion.(24,25) This modality is more portable than fluoros-copy and it has the benefit of being free of ionizing radiation. Ultrasound is also noninvasive. These advantages make diaphragmatic ultrasound more attractive especially for young adults or mechanically ventilated patients. (26)

Figur-1.1a Probe position for B and M mode diaphragmatic thickness measurements in the zone of apposition with 10–12 MHz probe. 1. b B-mode sonography of the diaphragm in the zone of apposition. A-Echogenic diaphragmatic pleura, B-non-echogenic central layer, C-echogenic peritoneal layer. Notice the thickness measurement of each layer

Diaphragmatic atrophy can be diagnosed on ultrasonographic basis as diaphragmatic thickness <20 mm (27).

However, ultrasonography has few limita-tions. It is operator dependent and requires significant expertise, as the field of view is often small and may suffer from intervening lung or bowel air. These organs can obscure diaphragmatic movement, making assessment of diaphragm function difficult. (28)

The aim of the work:

To evaluate diaphragmatic thickness using ultrasonography in mechanically ventilated patients on different modes of ventilation and its change overtime.

Patients and Methods

This study was carried out on 67 adult patients of both genders who were admitted to Critical Care Medicine Department in Alexandria main university hospital over a period of six months starting from 1/4/2014.

All haemodynamically stable adult Patients who required mechanical ventilation with positive end-expiratory pressure level ≤ 5 cm H_2O were included in the study.

Some patients were excluded for reasons as: history of diaphragmatic or neuromuscular disease (myasthenia gravis, Guillain-Barre´ syndrome, and amyotrophic lateral sclerosis), use of any muscle-paralyzing agent, use of aminoglycosides and corticosteroids, morbid obesity (body mass index > 40), current thoracotomy, pneumothorax or pneumo-mediastinum, declined consent, or respiratory rate ≥ 30 breaths/min.

Approval of the Medical Ethics Committee of Alexandria faculty of Medicine and an informed consent from the patient̕s next of kin was taken before conducting the study.

All patients included in the study were subjected after admission to the followings:

- Complete history taking including medical and surgical history.
- Complete physical examination.
- Chest ultrasonography using ultrasound unit, digital ultrasonic imaging system Model DP3300, (SHELZHEN MINDRAY) biomedical electronic CO.LTD with macro convex probe 2.5-5 MHZ :

1. Patients on all modes of ventilation were included and trends in changes in diaphragm thickness within groups (Controlled modes, assisted modes and spontaneous modes) were determined.
2. As a control for generalized muscle wasting in the critically ill, we acquired daily ultrasonographic images of the quadriceps muscle from each subject over the period of the study.
3. Daily ultrasonographic images of the diaphragm by placing Probe over one of the lower intercostal spaces in the right anterior axillary line for the right diaphragm with the probe fixed on the chest wall during respiration; the ultrasound beam was directed to the hemidiaphragmatic domes at an angle of not < 70°.
4. Diaphragmatic thickness was measured once per day as soon as possible after consent granted and continued until weaning trial whatever it

resulted in successful or failed weaning, discharge or death, whichever came first.
5. All measurements were performed during tidal breathing at 6–12 mL/kg, excluding smaller or deeper breaths.
6. The whole ultrasound examination was accomplished in 5 minutes.
7. Ultrasonographic diaphragmatic atrophy was diagnosed if thickness was < 20 mm.

- Outcome parameters included :
1. **Successful weaning:** defined as a state in which a patient was able to maintain his or her own breathing for 48 hours without any level of ventilator support.
2. **Primary weaning failure:** defined as Requirement for mechanical ventilation within 48 hours of self-breathing.
3. **Secondary weaning failure:** defined as requirement for mechanical ventilation after a successful weaning, i.e., respiratory failure occurring past the 48 hours of self-breathing.
4. **Total ventilation time:** defined as the period between the start and end of mechanical ventilation.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 15.0. Qualitative data were described using number and percent. Quantitative data were described using minimum and maximum, mean and standard deviation and median.

Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test or Monte Carlo correction.

The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used.

For normally distributed data, comparison between two independent population were done using independent t-test while more than two population were analyzed F-test (ANOVA). For abnormally distributed data, comparison between two independent populations were done using Mann Whitney test while Kruskal Wallis test was used to compare between different groups. Significance of the obtained results was judged at the 5% level.

Results & Discussions

This study was conducted on 67 mechanically ventilated patients admitted to the Critical Care Medicine Department in Alexandria Main University Hospital.

Table-1. Effect of different modes of mechanical ventilation on diaphragmatic atrophy.

	Modes						χ^2	p
	Controlled (n=19)		Assisted (n=23)		Spontaneous (n=25)			
	No.	%	No.	%	No.	%		
Diaphragmatic atrophy								
Diaphragmatic atrophy	15	78.9	14	60.9	1	4.0	28.192[*]	<0.001[*]
No diaphragmatic atrophy	4	21.1	9	39.1	24	96.0		
Sig. bet. groups	p_1 <0.001[*], p_2 = 0.207, p_3 <0.001[*]							

χ^2: Chi square test
p_1: p value for comparing between Controlled and Spontaneous
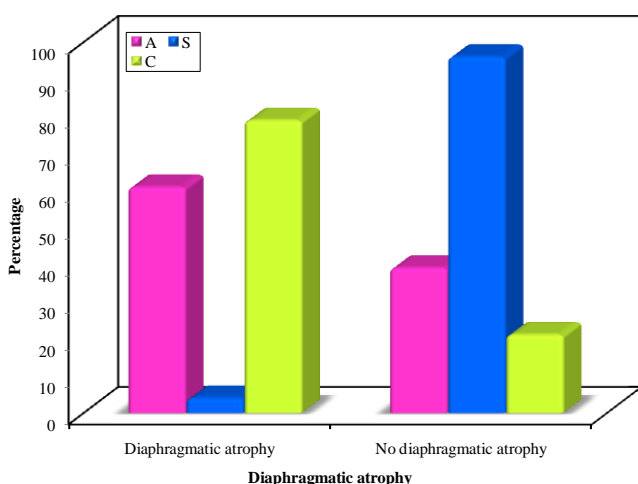p_2: p value for comparing between Assisted and Controlled
p_3: p value for comparing between Assisted and Spontaneous
    *: Statistically significant at $p \leq 0.05$

Patients were divided into three main groups;, Group I: patients on Controlled mechanical ventilation modes, Group II: patients on Assisted mechanical ventilation mode and Group III: patients on spontaneous mechanical ventilation modes. Patients were further divided into two groups; Group A: patients with diaphragmatic atrophy and Group B: patients without diaphragmatic atrophy.

Among patients on controlled modes 4 patients (21.1%) hadn`t developed diaphragmatic atrophy while 15 patients (78.9%) had developed diaphragmatic atrophy as shown in table (1) and figure (2).

Figure-2.Effect of different modes of mechanical ventilation on diaphragmatic atrophy.

Among patients on assisted modes 9 patients (39.1%) hadn`t developed diaphragmatic atrophy while 14 patients (60.9%) had developed diaphragmatic atrophy as shown in table (1) and figure (2).

While patients on spontaneous modes of mechanical ventilation 24 patients (96.0%) hadn`t developed diaphragmatic atrophy while 1 patient (4.0%) had developed diaphragmatic atrophy as shown in table (1) and fig (2).

Controlled and assisted modes were associated with significantly higher rates of diaphragmatic atrophy than spontaneous modes while there was no significant difference regarding diaphragmatic atrophy between controlled and assisted modes as shown in table (1) and fig. (2).

Regarding total mechanical ventilator days among the three groups; it ranged within 5.0 – 13.0 days with a mean 7.32 ± 2.0 days in controlled modes group, ranged within 4.0 – 12.0 days with a mean 7.04 ± 2.1 days in assisted modes group while ranged from 2.0 – 4.0 days with a mean 2.56 ± 0.77 days in spontaneous modes groups. There was a significant difference between controlled and spontaneous modes and between assisted and spontaneous modes while there was no significant difference between assisted and controlled modes groups as shown in table (2) and figure (3).

Regarding ICU days among the three groups; it ranged from 5.0 – 15.0 days with a mean 9.05 ± 2.95 days in patients on controlled modes, it ranged within 4.0 – 14.0 days with a mean 9.43 ± 2.57 days in patients on assisted modes and it ranged within 4.0 – 11.0 days with a mean 6.32 ± 1.86 days in patients on spontaneous modes. There was a significant difference between controlled and spontaneous modes and between assisted and spontaneous modes while there was no significant difference between assisted and controlled modes as shown in table (2) and figure (3).

Regarding effect of different modes of mechanical ventilation on mortality5 patients (26.3%) on controlled modes died; 3 patients (13.0%) on assisted modes died while no patients (0.0%) on spontaneous modes died so there was significant

Table-2. Correlation of mode of mechanical ventilation with total ventilatory days and ICU days

	Modes			KW χ^2	p
	Controlled (C) (n=19)	**Assisted (A) (n=23)**	**Spontaneous (S) (n=25)**		
MV days					
Min-Max.	5.0 – 13.0	4.0 – 12.0	2.0 – 4.0	46.27[*]	<0.001[*]
Mean±SD	7.32 ± 2.0	7.04±2.10	2.56±0.77		
Median	7.0	7.0	2.0		
Sig.bet. groups	p_1<0.001[*],p_2=0.847,p_3<0.001[*]				
ICU days					
Min-Max.	5.0 – 15.0	4.0-14.0	4.0 – 11.0	18.15[*]	<0.001[*]
Mean±SD	9.05± 2.95	9.43±2.57	6.32±1.86		
Median	9.0	9.0	6.0		
Sig. bet. grps	p_1<0.001[*],p_2=0.655,p_3=0.002[*]				

χ^2: Chi square test
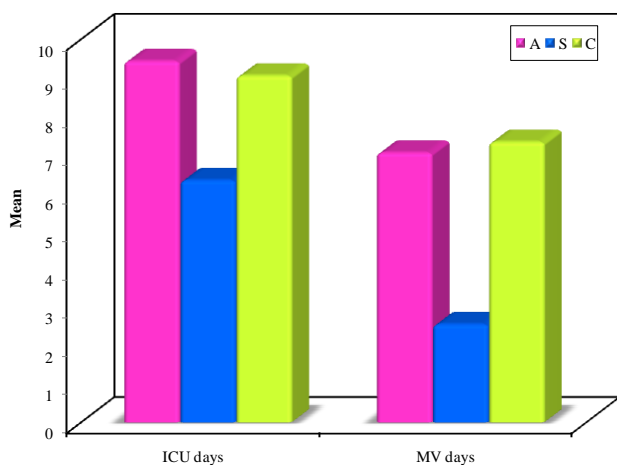p_1: p value for comparing between Controlled and Spontaneous
p_2: p value for comparing between Assisted and Controlled
p_3: p value for comparing between Assisted and Spontaneous
*: Statistically significant at p ≤ 0.05

difference between controlled and spontaneous modes while there was no significant difference between assisted and controlled modes and between assisted and spontaneous modes as regard mortality as shown in table (3) and figure (4).

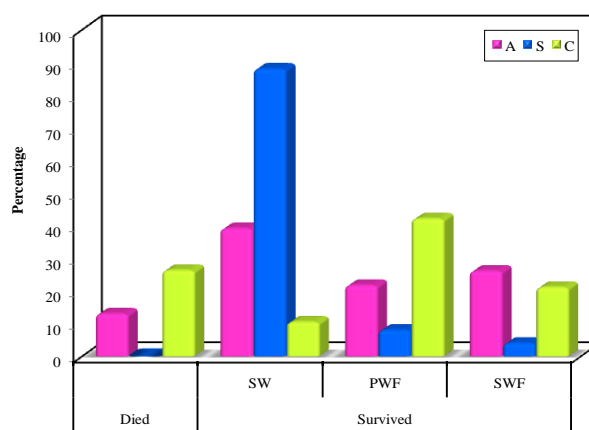**Figure-3. Correlation of mode of mechanical ventilation with total ventilatory days and ICU days.**

Among survived patients on controlled modes only 2 patients (10.5%) were successfully weaned, 4 patients (21.1%) suffered from secondary weaning failure and 8 patients (42.1%) suffered from primary weaning failure as shown in table (3) and figure (4).

While survived patients on assisted modes of mechanical ventilation 9 patients (39.1%) were successfully weaned, 6 patients (26.1%) suffered from secondary weaning failure and 5 patients (21.7%) suffered from primary weaning failure as shown in table (3) and figure (4).

And survived patients on spontaneous mode of 22 patients (88.0%) were successfully weaned, only one patient (4.0%) suffered from secondary weaning failure and only 2 patients (8.0%) suffered from primary weaning failure as shown in table (3) and figure (4).

There was significant difference between controlled and spontaneous modes and between assisted and spontaneous modes while there was no significant difference between assisted and controlled modes as regard weaning from mechanical ventilator as shown in table (3) and figure (4).

Figure-4. Association of mode of mechanical ventilation with outcome of patients.(SW: successful weaning, PWF: primary weaning failure, SWF: secondary weaning failure)

Regarding diaphragmatic thickness; it ranged within 1.84 – 2.57mm with a mean 2.19 ± 0.22mm in patients on assisted modes, it ranged within 1.8 – 2.43mm with a mean 2.18 ± 0.19 in patients on

Table-3. Association of mode of mechanical ventilation with outcome of patients

	Controlled (C) (n=19)		Assisted (A) (n=23)		Spontane-ous (S) (n=25)		χ^2	MCp
	No.	%	No.	%	No.	%		
Outcome								
Died	**5**	**26.3**	**3**	**13.0**	**0**	**0.0**	**7.251**[*]	**0.016**[*]
Survived	**14**	**73.7**	**20**	**87.0**	**25**	**100.0**		
Sig. bet. Groups	$p_1 = 0.102$, $p_2 = 0.433$, $p_3 = 0.011$[*]							
Successful weaning	2	10.5	9	39.1	22	88.0	23.069[*]	<0.001[*]
Primary weaning failure	8	42.1	5	21.7	2	8.0		
Secondary weaning failure	4	21.1	6	26.1	1	4.0		
Sig. bet. Groups	$p_1 = 0.008$[*], $p_2 = 0.102$, $p_3 < 0.001$[*]							

χ^2: Value for Chi square, MC: Monte Carlo test, Sig. bet. Grps was done using Monte Carlo test
p_1: p value for comparing between Controlled and Spontaneous modes.
p_2: p value for comparing between Controlled and Assisted modes.
p_3: p value for comparing between Assisted and Spontaneous modes.
*: Statistically significant at p ≤0.05

Table-4. Relation between Modes with Diaphragmatic thickness

	Controlled (C) (n=19)	Assisted (A) (n=23)	Spontaneous (S) (n=25)	F	p
Diaphragmatic thickness					
Min. – Max.	1.80 – 2.43	1.84 – 2.57	1.90 – 2.96	13.376[*]	<0.001[*]
Mean ± SD.	2.18 ± 0.19	2.19 ± 0.22	2.49 ± 0.27		
Median	2.18	2.14	2.45		
Sig. bet. groups	$p_1 < 0.001$[*], $p_2 = 0.958$, $p_3 < 0.001$[*]				

F: F test (ANOVA), Sig. bet. grps was done using Post Hoc Test (LSD)
p_1: p value for comparing between C and S
p_2: p value for comparing between C and A
p_3: p value for comparing between A and S
*: Statistically significant at p ≤ 0.05

controlled modes and it ranged within 1.90 – 2.96mm with a mean 2.49 ± 0.27mm in patients on spontaneous mode. There was a significant difference between assisted and spontaneous modes and between controlled and spontaneous modes while there was no significant difference between assisted and controlled modes as shown in tables (4) and figure (5).

Diaphragmatic thickness of patients on controlled mode of mechanical ventilation decrease 0.094mm/day (3.8%per day), while patients on assisted mode of mechanical ventilation decrease 0.091mm/day (3.6%per day), and while patients on spontaneous mode of mechanical ventilation increase 0.04mm/day (1.6% per day).

Regarding quadriceps thickness; it ranged within 13.62 – 24.88mm with a mean 18.64 ± 2.46mm in patients on assisted modes, it ranged within 16.13 – 21.82mm with a mean 18.48 ± 1.52 in patients on controlled modes and it ranged within 12.30 – 25.40mm with a mean 17.82 ± 3.09mm in patients on spontaneous mode. Quadriceps thickness of patients on controlled, assisted and spontaneous modes of mechanical ventilation decrease 0.664 mm per day (3.44% per day).There wasn`t a significant difference as regard quadriceps thickness between three modes of mechanical ventilation as shown in table (5) and figure (6).

Regarding total mechanical ventilator days; it ranged within 2.0 – 10.0 days with a mean 4.32 ± 2.44 days in patients who hadn`t developed diaphragmatic atrophy, while it ranged from 4.0 – 13.0 days with a mean 7.23 ± 2.39 days in patients who had developed diaphragmatic atrophy. There was a significant difference between the two groups as shown in table (4) and figure (5).

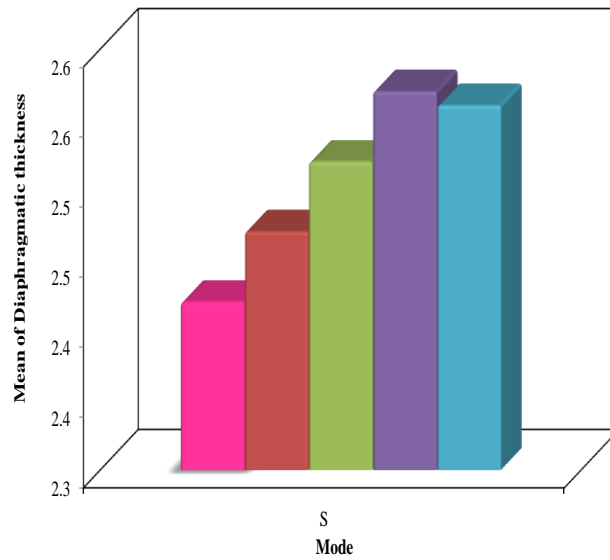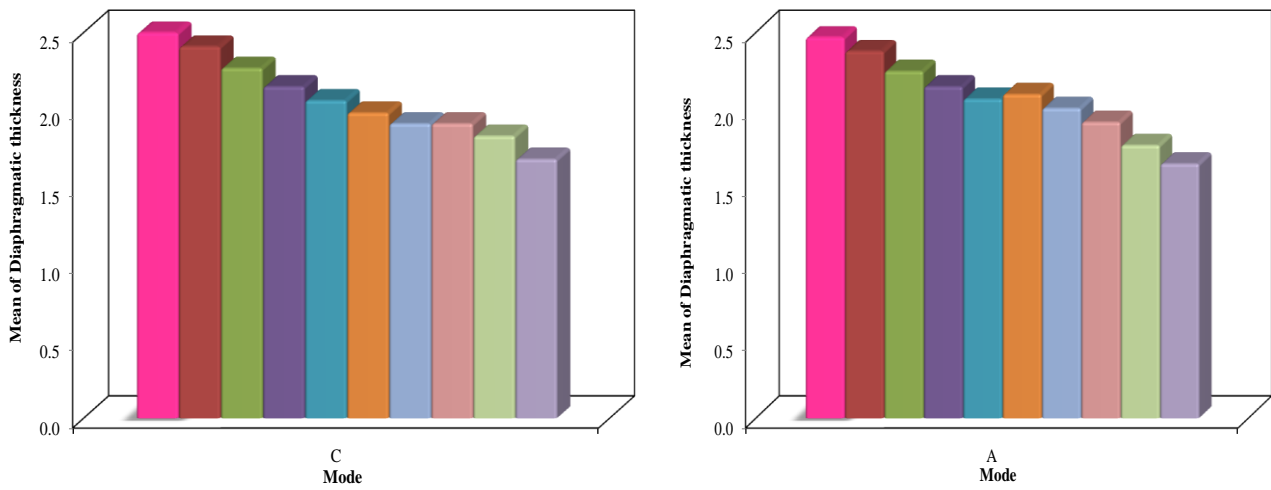**Figure-5. Comparison between different modes according to Diaphragmatic thickness.**

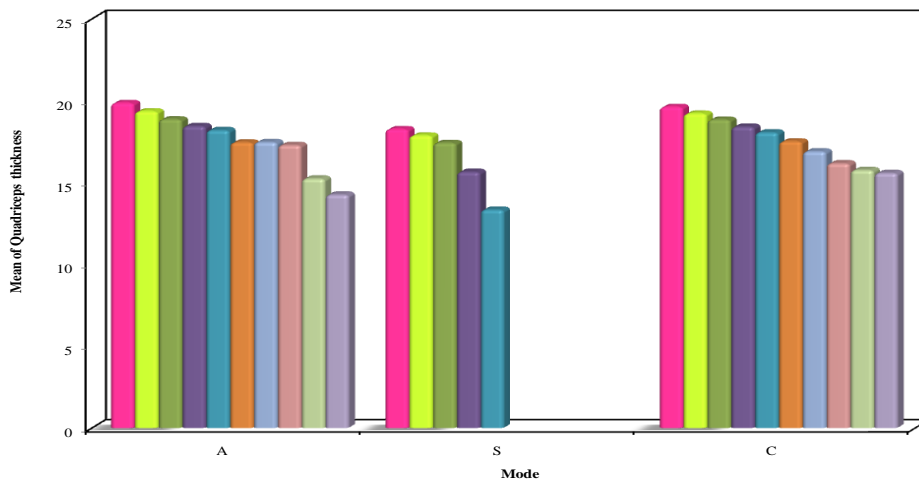**Figure-6. Comparison between different modes according to Quadriceps thickness**

Table-5. Relation between Modes with Quadriceps thickness .

	Modes			F	P
	Controlled (C) (n=19)	Assisted (A) (n=23)	Spontaneous (S) (n=25)		
Quadriceps thickness					
Min. – Max.	16.13-21.82	13.62–24.88	12.30 -25.40	0.709	0.496
Mean ± SD.	18.48 ± 1.52	18.64 ± 2.46	17.82 ± 3.09		
Median	18.21	18.13	17.20		

F: F test (ANOVA)

Table-6. Effect of diaphragmatic atrophy on total mechanical ventilator days and ICU days

	Diaphragmatic Atrophy (n = 30)	No diaphragmatic atrophy (n = 37)	Z	P
ICU days				
Min. – Max.	4.0 – 15.0	4.0 – 14.0	2.159[*]	0.031[*]
Mean ± SD	9.08 ±2.91	7.59± 2.63		
Median	9.0	7.0		
MV days				
Min. – Max.	4.0 – 13.0	2.0 – 10.0	4.149[*]	<0.001[*]
Mean ± SD	7.23± 2.39	4.32± 2.44		
Median	7.0	3.0		

Z: Z for Mann Whitney test
*: Statistically significant at $p \leq 0.05$

Table-7. Effect of diaphragmatic atrophy on mortality and weaning

	Diaphragmatic atrophy (n = 30)		No diaphragmatic atrophy (n = 37)		χ^2	P
	No.	%	No.	%		
Outcome						
Died	5	16.7	3	8.1	1.154	[FE]p= 0.451
Survived	25	83.3	34	91.9		
Successful weaning	3	12.0	30	81.1	34.031[*]	[MC]p <0.001[*]
Secondary weaning failure	9	36.0	2	5.4		
Primary weaning failure	13	52.0	2	5.4		

χ^2: Chi square test
MC: Monte Carlo test
FE: Fisher Exact test
*: Statistically significant at $p \leq 0.05$

Regarding ICU days; it ranged within 4.0 – 14.0 days with a mean 7.59 ± 2.63 days in patients who hadn`t developed diaphragmatic atrophy while it ranged within 4.0 – 15.0 days with a mean 9.08 ± 2.91 days in patients who had developed diaphragmatic atrophy. There was a significant difference between the two groups as shown in table (4) and figure (5).

Among patients who had developed diaphragmatic atrophy 5 patients (16.7%) died while among patients who hadn`t developed diaphragmatic atrophy 3 patients (8.1%) died. there wasn`t a significant difference as regard mortality between the two groups as shown in table (5) and figure (6).

Patients who had developed diaphragmatic atrophy and survived only 3 patients (12.0%) were

successfully weaned, 9 patients (36.0%) suffered from secondary weaning failure and 13 patients (52.0%) suffered from primary weaning failure while among patients who hadn`t developed diaphragmatic atrophy and survived 30 patients (81.1%) were successfully weaned, only 2 patients (5.4%) suffered from secondary weaning failure   and only 2 patients (5.4%) suffered from primary weaning failure so there was a significant difference between the two groups as regard weaning from mechanical ventilation as shown in table (5) and figure (6).

Figure-5. Relation between Diaphragmatic atrophy with ICU and MV days
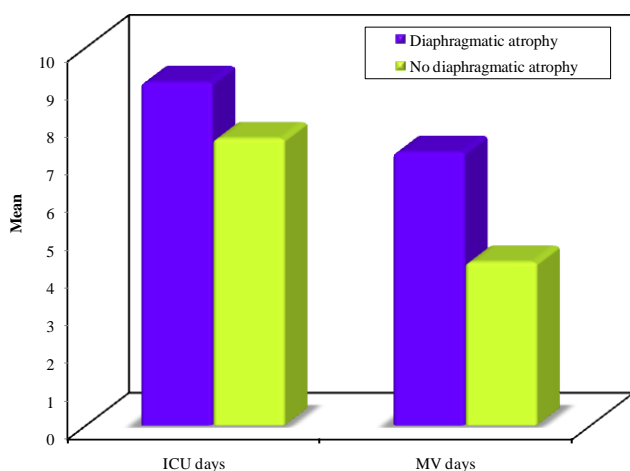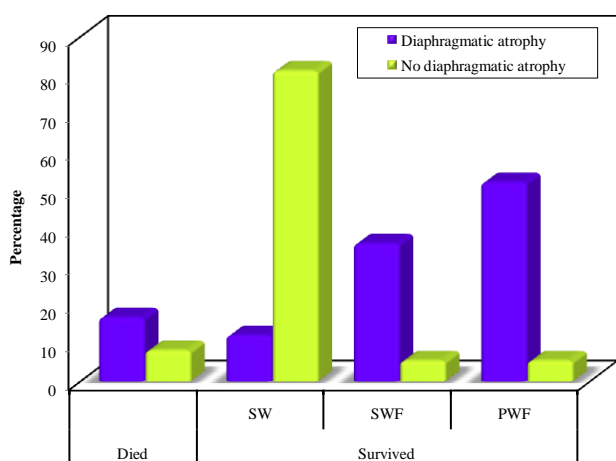

Figure-6. Effect of diaphragmatic atrophy on mortality and weaning

(SW: successful weaning, PWF: primary weaning failure, SWF: secondary weaning failure).

Discussion

The current study was a prospective observational study conducted on 67 mechanically ventilated patients admitted to the Critical Care

Medicine Department in Alexandria Main University Hospital in the period from 1\4\2014 to 30\9\2014.

Diaphragmatic and quadriceps thickness was measured daily in all mechanically ventilated patients using ultrasonography; results were recorded and correlated to mode of mechanical ventilation used. .

The current study used B-mode ultrasonography to evaluate diaphragm thickness in critically ill patients on MV in the ICU. The proposed multicenter study will focus on using diaphragm thickness, as determined by ultrasonography, as a predictor of weaning failure. This data will allow us to potentially identify at risk patients and allow caregivers to develop interventions that may effectively decrease the risk of poor weaning outcomes by mitigating this treatable mechanism of weaning failure**.**

In the present study we had three groups of critically ill patients according to mode of mechanical ventilation. Group I: patients on controlled mechanical ventilation mode (n=19), Group II: patients on assisted mechanical ventilation mode (n=23) and Group III: patients on spontaneous mechanical ventilation mode (n=25).

VIDD has been studied extensively over the past 25 years. In 1988 Knisely et al, [29] postulated that controlled MV predisposes diaphragm myofibers to atrophy in infants and neonates that were provided long-term ventilator assistance. Although provocative, this investigation did not provide direct evidence that controlled MV induces diaphragmatic atrophy. In 1994 Le Bourdelles et al,[30] revealed that 48 hours of controlled MV (i.e., full ventilator support of breathing) resulted in significant loss of diaphragmatic mass and a large reduction in maximal diaphragmatic specific force production. This original account was quickly supported by another study depicting the influence of prolonged controlled mandatory MV on in-vivo diaphragmatic function in healthy baboons [31]. This primate study concluded that prolonged controlled mandatory MV results in significant impairment of diaphragmatic contractile performance as indicated by a decrease in both maximal transdiaphragmatic pressure and diaphragmatic endurance [31]. Following these early investigations, scientific interest in the effects of MV on diaphragmatic structure and function grew rapidly, and numerous animal studies published in 2002–2003 consistently concluded that controlled mandatory MV results in the rapid development of both diaphragmatic atrophy and contractile dysfunction. [32-34].

While animal studies consistently indicated that controlled mandatory MV induces VIDD, the question of whether controlled mandatory MV produces VIDD in humans remained unknown until a milestone study published in 2008 revealed that controlled mandatory MV results in rapid diaphragmatic atrophy in humans [16]. These findings have now been confirmed by other groups, and together, these studies clearly demonstrate that controlled mandatory MV results in

the rapid development of both diaphragmatic atrophy and contractile dysfunction in humans [9,35].

Ventilator-induced diaphragm dysfunction (VIDD) define as mechanical ventilation that cause diaphragmatic atrophy (diaphragmatic thickness <20 mm) and contractile dysfunction or diaphragmatic vertical excursion <10 mm or paradoxical movements [27,36].

In this study, the age of the studied patients ranged within 36.0 – 92.0 years. The mean was 65.88 ± 10.59 years. 39 patients were males (58.2%) and 28 patients were females (41.8%). There were no significant differences between the three groups regarding age, sex distribution, past medical history and smoking history, as shown in the study by Andrea J.Boon et al [37], who showed that the diaphragmatic thickness and contractility not affected with age, gender, past medical history and smoking history when ultrasound applied on 150 normal breathing persons.

In the current study, the ultrasonographic recording of the right hemidiaphragmatic thickness was found to be easier than the left side. Indeed, increased respiratory effort can result in greater chest wall movement and cause the ribs and lung to obscure the images in patients with dyspnea. Ewan C. Goligher et al [38]. showed that Ultrasound measurements of right hemidiaphragm thickness are feasible and highly reproducible when Five observers measured diaphragm thickness (T di) and thickening (TFdi)in 96 mechanically ventilated patients and Right hemidiaphragm thickness was obtained on 95 % of attempts; left hemidiaphragm measurements could not be obtained consistently. Scott et al [39] showed a 28% failure rate in attempting an ultrasonographic scan of the right hemidiaphragm. This was attributed to inclusion of larger tidal volumes in deep inspirations requiring more excursions.

Visualization of the left hemidiaphragm is recognized as more difficult due to the smaller window of the spleen as compared with the liver window. The position of the probe could not be readily adjusted as the spleen window is small.

In our study total ventilation days ranged within 5.0 – 13.0 days with a mean 7.32 ± 2.0days in controlled modes group, ranged within 4.0 – 12.0days with a mean 7.04 ± 2.10days in assisted modes group, while ranged from 2.0 – 4.0 days with a mean 2.56 ± 0.77days in spontaneous modes groups. There was a significant difference between assisted and spontaneous modes and between controlled and spontaneous modes while there was no significant difference between assisted and controlled modes.

Haitsma et al [40], concluded in his study that diaphragmatic dysfunction occurs in patients, especially when ventilated with controlled modes of ventilation that minimize diaphragm activity resulting in difficulties in weaning patients and prolonging time on the ventilator.

In current study patients there is Significant difference between the three groups regarding weaning from mechanical ventilation 63.2% of patients (12 patients) on controlled mechanical ventilation modes and 47.8% of patients (11 patients) on assisted mechanical ventilation modes suffered primary and secondary weaning failure while 88.0% of patients (22 patients) were successfully weaned from spontaneous mechanical ventilation.

Similarly in the pilot study which carried out by Francis et al, [41] on twenty critically ill patient who required MV for at least 72 hours to assess diaphragmatic thickness and its changes over time as a function of mode of mechanical ventilation, they postulated that unloading of the respiratory muscles and reduction in diaphragm activity occurs during controlled mechanical ventilation may lead to atrophy, diminished force generating capacity and consequently difficulties in weaning.

Also Yang L, et al, [42] concluded in their study that even short-term (2–4 days) imposition of CMV leads to major remodeling of the diaphragm. Such changes could contribute to the difficulties encountered in discontinuing ventilatory support in many patients, particularly after more prolonged periods of mechanical ventilation.

While the study by Brochard et al [43], involving 456 randomized patients showed that spontaneous mode of mechanical ventilation has less weaning failure rate than controlled and intermittent modes and has also shorter duration of weaning.

In this study diaphragmatic thickness; it ranged within 1.84 – 2.57mm with a mean 2.19 ± 0.22mm in patients on assisted modes, it ranged within 1.8 – 2.43mm with a mean 2.18 ± 0.19 in patients on controlled modes and it ranged within 1.90 – 2.96mm with a mean 2.49 ± 0.27mm in patients on spontaneous mode. There was a significant difference between assisted and spontaneous modes and between controlled and spontaneous modes while there was no significant difference between assisted and controlled modes.

In current study diaphragmatic thickness of patients on assisted mode of mechanical ventilation decrease 0.091mm/day (3.6%per day), while patients on controlled mode of mechanical ventilation decrease 0.094mm/day (3.8%per day), and while patients on spontaneous mode of mechanical ventilation increase 0.04mm/day (1.6%per day).In agreement of the study of by Colin Anthony Francis et al [41], mean increase in diaphragm thickness mean increase of 0.04±0.03mm per day (1.5±1.4% per day) in all 8 patients on PS ventilation. While 4 patients ventilated on assisted, controlled modes showed a mean decrease of 0.1±0.1mm per day (4.7±5.7% per day).

In current study quadriceps thickness of patients on assisted, controlled and spontaneous modes of mechanical ventilation decrease 0.664 mm per day (3.44% per day). In agreement of the study of by

Francis et al [41], mean decline in quadriceps thickness for all patients in his study is 2.0±2.7% per day.

Francis et al [41], showed that the rate of increase in diaphragm thickness in patients on pressure support was 1.5±1.4% per day, which was 1/3rdthe rate of decline seen in the patient ventilated on assisted, controlled modes (4.7±5.7% per day). These results suggest that recovery from the effects of ventilator-associated diaphragm atrophy will require more time than what was necessary for the atrophy to occur. Since diaphragm atrophy is associated with weakness, this relatively slow recovery may prolong weaning time of patients ventilated on mandatory modes of ventilation for prolonged periods.

Francis et al [41], Gerovasili et al [44] showed that the quadriceps muscles of the patients in this study showed a mean rate of decline of 2% per day. In contrast, there was a mean decline in diaphragm thickness of 4.7% per day in patients supported on assisted, controlled modes of ventilation. These findings suggest that the rapid decline in muscle thickness in critically ill patients who require assisted, controlled modes of ventilation may be limited to the diaphragm.

In current study, Regarding effect of different modes of mechanical ventilation on diaphragmatic atrophy there was a significant difference between assisted and spontaneous modes and between controlled and spontaneous modes while there was no significant difference between assisted and controlled modes, as Among patients on assisted modes 9 patients(39.1%) hadn`t developed diaphragmatic atrophy while 14 patients(60.9%) had developed diaphragmatic atrophy while, Among patients on controlled modes 4 patients(21.1%) hadn`t developed diaphragmatic atrophy while 15 patients(78.9%) had developed diaphragmatic atrophy, and among patients on spontaneous modes of mechanical ventilation 24 patients(96.0%) patients hadn`t developed diaphragmatic atrophy while one patients(4.0%) of patients had developed diaphragmatic atrophy. In agreement with our study Rita Galeiras Vázquez et al [45], showed that patients with spinal cord injury who need MV support, Diaphragmatic atrophy occurs early after only 18 hours of inactivity, VIDD has been linked to diaphragmatic inactivity caused by controlled and assisted ventilation, while spontaneous modes attenuate VIDD.

Sassoon et al [46] concluded in their study on 30 sedated mechanically ventilated rabbits that diaphragmatic contractility did not decrease with continuous positive airway pressure but decreased to 63% after 1 day of CMV and to 49% after 3 days of CMV. After 3 days of CMV, significant myofibril damage occurred in the diaphragm.

Jaber et al [9], Powers et al. [36], who showed that full support MV results in the rapid activation of proteases in diaphragm myofibres which is associated with diaphragm atrophy in both humans and animals.

In the study of Jung et al, [47] Two groups of six anesthetized piglets were ventilated during a 72 hours period. Piglets in the CMV group were ventilated without spontaneous ventilation, and piglets in the ASV group were ventilated with spontaneous breaths. After 72 h of ventilation, transdiaphragmatic pressure decreased by 30% of its baseline value in the CMV group, whereas it did not decrease in the ASV group. Although CMV was associated with an atrophy of the diaphragm (evaluated by mean cross-sectional area of both the slow and fast myosin chains), atrophy was not detected in the ASV group. Consistently with our results they concluded that maintaining diaphragmatic contractile activity by using the spontaneous mode may protect the diaphragm against the deleterious effect of prolonged controlled mandatory ventilation.

Same results were obtained by Levine et al, [48] who concluded that combination of 18 to 69 hours of complete diaphragmatic inactivity and controlled mandatory ventilation results in marked atrophy of human diaphragm myofibers

In the study of Shanely RA, et al [34]; adult female Sprague-Dawley rats who were tracheostomized and mechanically ventilated developed diaphragmatic contractile dysfunction and atrophy after 18 hours of CMV.

Consistently with our results; Hudson et al, [10] concluded in their study that both high level pressure support (assisted mechanical ventilation) ventilation and controlled mechanical ventilation induce diaphragmatic dysfunction and atrophy.

In concordance with to our findings; Forty-two adult Sprague-Dawley rats had intraperitoneal anesthesia and were randomly assigned to the control group or to receive 6 or 18 hours of CMV or PSV. In-vitro proteolysis and protein synthesis were measured on the costal region of the diaphragm. From that Futier et al, [49], could conclude that PSV is efficient at reducing mechanical ventilation-induced proteolysis and inhibition of protein synthesis without modifications in the level of oxidative injury compared with CMV. PSV could be an interesting alternative to limit ventilator-induced diaphragmatic dysfunction.

Sassoon et al [46] assessed in-vitro diaphragmatic isometric and isotonic contractile function in sedated rabbits which were randomized equally into control animals, those with 3 days of assisted ventilation, and those with controlled ventilation; they concluded that assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction which is non-concordant with our results, it may be because of the difference between both studies in ventilatory days; which ranged from 2.0 to 13.0 days with a mean 6.93 ± 3.15 days.

The mechanisms of VIDD have not been fully elucidated. Muscle atrophy, oxidative stress, and structural injury have been documented after CMV [31]. Muscle proteolysis is a highly regulated process accomplished by at least three different proteolytic systems: the ubiquitin-proteosome pathway, the

calcium-dependent system, and the lysosomal system. All three proteolytic systems have been shown to be implicated in the increased diaphragmatic proteolysis observed after CMV, as indicated by changes in the gene expression profile of several proteolytic enzymes. [46]

MV-induced oxidative stress is also an important contributor to both MV-induced proteolysis and contractile dysfunction. Indeed, Shanely and colleagues [34] have shown that MV is associated with a rapid onset of protein oxidation in diaphragm fibers. This is significant because oxidative stress has been shown to promote disuse muscle atrophy [50] and has been directly linked to activation of the ubiquitin-proteasome system of proteolysis. [51] The precise contribution of each factor to the development of VIDD and their kinetic of apparition has yet to be defined.

Our results revealed that only 3 patients (12.0%) of those who developed diaphragmatic atrophy were successfully weaned in comparison to 22 patients (88.0%) suffered from primary and secondary weaning failure. While 30 patients (81.1%) of those who did not develop diaphragmatic atrophy were successfully weaned, in comparison to only 4 patients (10.8%) suffered from primary and secondary weaning failure which represents a significant difference between the two groups.

In agreement of our study Jubran et al.[52] showed that the decrease in diaphragmatic contractility observed during controlled ventilation contributes to failure to wean from the ventilator,

The study of Won Young Kim, et al.[53] who found that the diaphragmatic dysfunction group showed higher rates than non- diaphragmatic dysfunction group as regard primary (83% versus 59% respectively) and secondary (50% versus 22% respectively)weaning failure.

Consistently with our findings; Petrof, et al, [9] concluded in their study that diaphragmatic dysfunction is common in mechanically ventilated patients and is a likely cause of weaning failure.

Won Young Kim, et al [53] studied prevalence of ultrasonographically diagnosed diaphragmatic dysfunction in Eighty-eight consecutive patients in the medical intensive care unit who required mechanical ventilation over 48 hours and found that patients with ventilator induced diaphragmatic dysfunction had longer weaning time and higher rates of primary and secondary weaning failure which is concordant to our results.

Similarly to our study`s results, Supinski, et al, [54] measured diaphragmatic strength in adult ICU patients who required mechanical ventilation in the University of Kentucky MICU for more than 24 hours and found that diaphragmatic weakness was associated with poor patient outcomes, including a significantly longer duration required for weaning from mechanical ventilation

Against our study, Laghi et al .[18] measured twitch transdiaphragmatic pressure using phrenic nerve stimulation in 11 weaning failure and 8 weaning success patients relieved that, weaning failure was not accompanied by low-frequency fatigue of the diaphragm, although many weaning failure patients displayed diaphragmatic weakness.

As regard the total mechanical ventilation duration has been found to be shorter in the non-diaphragmatic atrophy group than in the diaphragmatic atrophy group (with mean 4.32±2.44 vs. 7.23 ± 2.39). This has been compared to the study Won Young Kim, et al.[53] where it was also increased by mean 8.45 (4.54 - 17) in the non- diaphragmatic atrophy group versus 24 (15.58 - 35.4) in the diaphragmatic atrophy group which was also found to be of statistical significance. And in agreement of our study Supinski et al [118] and Greet Hermans et al [35] showed that patients with diaphragmatic weakness had a markedly worse prognosis when diaphragmatic force measured by transdiaphragmatic pressure measurements during bilateral magnetic stimulation of the phrenic nerves. This consisted not only of a more prolonged need for ventilator support.

In the study of Won Young Kim, et al.[53] it was found that patients with diaphragmatic dysfunction had longer ventilatory time than other patients without diaphragmatic dysfunction which is concordant to our findings.

This may explained by Pedro A Mendez et al [55] who showed that disuse atrophy is the result of complex mechanisms, including altered protein turnover and disturbed redox signaling. The result of these ICU-acquired complications is longer duration of MV, prolonged ICU and hospital stay, and poorer functional status at hospital discharge.

In the current study, it had been found that the median for the ICU stay was 7 days in the non-diaphragmatic atrophy group in comparison to 9 days in the diaphragmatic atrophy group which was of statistical significance. In agreement with our current study, Won Young Kim, et al [53] found longer days of ICU stay in the diaphragmatic dysfunction group, than in non- diaphragmatic dysfunction group.

In the above mentioned study of Supinski G, et al,[54] it was found that diaphragmatic weakness was associated with poor patient outcomes, including a significantly increased hospital stay and transfer to Long term acute care hospitals which is similar to our results.

As regard the hospital mortality there was no statistical difference between the two groups, in the study of Won Young Kim, et al. [53] there was also any statistical difference in the study as regard the mortality.

Against our results; Supinski G, et al, [54] found in his above mentioned study that VIDD is associated with poor patient outcomes, including a significantly increased mortality.

Conclusion

- MV induces diaphragmatic atrophy which is significantly higher with Controlled and assisted mechanical ventilation modes in comparison to spontaneous modes.
- Controlled and assisted mechanical ventilation modes are associated with higher rates of primary and secondary weaning failure in comparison to spontaneous modes.
- Controlled and assisted mechanical ventilation modes are associated with more ventilatory days and longer hospital stay in comparison to spontaneous modes.
- Progressive diaphragmatic atrophy, detected by B-mode Ultrasonography, is associated with high sensitivity, specificity, positive and negative predictive values to determine weaning failure in addition to association with prolonged duration of mechanical ventilation as well as prolonged ICU stay, for patients on different mode of mechanical ventilation.

Conflict of Interests:

Authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Vasilyev S, Schaap RN, Mortensen JD. Hospital survival rates of patients with acute respiratory failure in modern respiratory intensive care units. An international, multicenter, prospective survey. Chest 1995;107(4):1083-8.
2. Martin L. Respiratory failure. Med Clin N Am 1997;61:1369.
3. British Thoracic Society Standards of Care Committee. Non-invasive ventilation in acute respiratory failure. Thorax 2002;57:192-211.
4. Health Sciences Authority (HSA), Health Products Regulation Group, Blood Services Group, Applied Sciences Group. Gn-13: guidance on the risk classification of general medical devices, revision 1.1. Singapore: HAS; 2014.
5. Saydain G, Islam A, Afessa B, Ryu JH, Scott JP, Peters SG. Outcome of patients with idiopathic pulmonary fibrosis admitted to the intensive care unit. Am J Respir Crit Care Med 2002;166(6):839-42.
6. Hess DR. Approaches to conventional mechanical ventilation of the patient with acute respiratory distress syndrome. Respir Care 2011; 56 (10): 1555–72.
7. Hoesch RE, Lin E, Young M, Gottesman RF, Altaweel L, Nyquist PA, et al. Acute lung injury in critical neurological illness. Crit Care Med 2012;40(2):587-93.
8. Konrad F, Schreiber T, Brecht-Kraus D, Georgieff M. Mucociliary transport in ICU patients. Chest 2004; 105 (1): 237–41.
9. Petrof BJ, Jaber S, Matecki S. Ventilator-induced diaphragmatic dysfunction. Curr Opin Crit Care 2010; 16:19–25.
10. Hudson MB, Smuder AJ, Nelson WB. Both high level pressure support ventilation and controlled mechanical ventilation induce diaphragm dysfunction and atrophy. Critical Care Medicine 2012; 40:1254–60.
11. Santanilla JI1, Daniel B, Yeow ME. Mechanical ventilation. Emerg Med Clin North Am 2008; 26(3):849-62.
12. Brash JC, Jamieson ED. Cunningham's textbook of anatomy. 7thed. New York: Oxford University Press; 1937. Quoted from: Rives JD, Baker DD. Anatomy of the Attachments of the Diaphragm: Their Relation to the Problems of the Surgery of Diaphragmatic Hernia. Ann Surg 2002;115(5):745-55.
13. Tobin MJ, Laghi F, Brochard L. Role of the respiratory muscles in acute respiratory failure of COPD: lessons from weaning failure. J Appl Physiol 2009; 107:962–70.
14. Gibson GJ. Diaphragmatic paresis: pathophysiology, clinical features, and investigation. Thorax 2009; 44:960–70.
15. Chetta A. Chest radiography cannot predict diaphragm function. Respir Med 2005; 99:39–44.
16. Nason LK. Imaging of the diaphragm: anatomy and function. Radiographics 2012; 32:E5170.
17. Alexander C. Diaphragm movements and the diagnosis of diaphragmatic paralysis. Clin Radiol 2006; 17:79–83.
18. Laghi F, Tobin MJ. Disorders of the respiratory muscles. Am J Respir Crit Care Med 2003; 168:10–48.
19. Davis J. Diaphragm function and alveolar hypoventilation. Q J Med 2006; 45:87–100.
20. Gierada DS, Curtin JJ, Erickson SJ, Prost RW, Strandt JA, Goodman LR. Diaphragmatic motion: fast gradientrecalled-echo MR imaging in healthy subjects. Radiology 2005; 194:879–84.
21. Kiryu S. Quantitative analysis of the velocity and synchronicity of diaphragmatic motion: dynamic MRI in different postures. Magn Reson Imaging 2006; 24:1325–32.
22. Beaulieu Y, Marik PE. Bedside ultrasonography in the ICU: part1. Chest 2005; 128:881-95.
23. Kim WY, Suh HJ, Hong SB, Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Crit Care Med 2011; 39:2627-30.
24. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography:

methods, reproducibility, and normal values. Chest 2009; 135:391-400.

25. Kim SH, Na S. An evaluation of diaphragmatic movement by M-mode sonography as a predictor of pulmonary dysfunction after upper abdominal surgery. Anesth Analg 2010; 110:1349-54.

26. Gerscovich EO, Cronan M, McGahan JP, Jain K, Jones CD, McDonald C. Ultrasonographic evaluation of diaphragmatic motion. J Ultrasound Med 2001; 20:597–604.

27. Sarwal A, Walker FO, Cartwright MS. Neuromuscular ultrasound for evaluation of the diaphragm. Muscle Nerve 2013; 47: 319-29.

28. Schabrun S, Chipchase L. Healthcare equipment as a source of nosocomial infection: a systematic review. J Hosp Infect 2006; 63: 239–45.

29. Knisely AS, Leal SM, Singer DB. Abnormalities of diaphragmatic muscle in neonates with ventilated lungs. J Pediatr 1988; 113: 1074–7.

30. Le Bourdelles G, Viires N, Boczkowski J, Seta N, Pavlovic D, Aubier M. Effects of mechanical ventilation on diaphragmatic contractile properties in rats. Am J Respir Crit Care Med 1994;149(6):1539-44.

31. Anzueto A, Peters JI, Tobin MJ, de los Santos R, Seidenfeld JJ, Moore G, et al. Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. Crit Care Med 1997;25(7):1187-90.

32. Criswell DS, Shanely RA, Betters JJ, McKenzie MJ, Sellman JE, Van Gammeren DL, et al. Cumulative effects of aging and mechanical ventilation on in vitro diaphragm function. Chest 2003; 124: 2302–8.

33. Gayan-Ramirez G, de Paepe K, Cadot P, Decramer M. Detrimental effects of short-term mechanical ventilation on diaphragm function and IGF-I mRNA in rats. Intensive Care Med 2003; 29: 825–33.

34. Shanely RA, Coombes JS, Zergeroglu AM, Webb AI, Powers SK. Short-duration mechanical ventilation enhances diaphragmatic fatigue resistance but impairs force production. Chest 2003; 123: 195–201.

35. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care 2010;14(4):R127.

36. Powers SK, Wiggs MP, Sollanek KJ, Smuder AJ. Ventilator-induced diaphragm dysfunction: cause and effect. Am J Physiol Regul Integr Comp Physiol 2013; 305(5):R464-77.

37. Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ. Two-dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects. Muscle Nerve 2013;47(6):884-9.

38. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 2015;41(4):642-9.

39. Scott S, Fuld JP, Carter R, McEntegart M, MacFarlane NG. Diaphragm ultrasonography as an alternative to whole-body plethysmography in pulmonary function testing. J Ultrasound Med 2006;25(2):225-32.

40. Haitsma JJ. Diaphragmatic dysfunction in mechanical ventilation. Curr Opin Anaesthesiol 2011;24(2):214-8

41. Francis CA. Serial ultrasonographic evaluation of diaphragm thickness during mechanical ventilation in ICU patients. Master Thesis. Department of Biomedical Physiology and Kinesiology, University of west Indies; 2013.

42. Yang, Luo J, Bourdon J, Lin MC, Gottfried DB, Petrof BJ. Controlled mechanical ventilation leads to remodeling of the rat diaphragm. Am J Respir Crit Care Med 2002; 166(8): 1135-40.

43. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am J Respir Crit Care Med 1994;150(4):896-903.

44. Gerovasili V, Stefanidis K, Vitzilaios K, Karatzanos E, Politis P, Koroneos A, et al. Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomized study. Crit Care 2009;13(5):R161.

45. Galeiras Vazquez R, Rascado Sedes P, Mourelo Farina M, Montoto Marques A, Ferreiro Velasco ME. Respiratory management in the patient with spinal cord injury. Biomed Res Int 2013;2013:168757.

46. Sassoon CS, Caiozzo VJ, Manka A, Sieck GC. Altered diaphragm contractile properties with controlled mechanical ventilation. J Appl Physiol 2002; 92: 2585–95.

47. Jung B, Constantin JM, Rossel N, Le Goff C, Sebbane M, Coisel Y, et al. Adaptive support ventilation prevents ventilator-induced diaphragmatic dysfunction in piglet: an in vivo and in vitro study. Anesthesiology 2010;112(6):1435-43.

48. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 2008; 358 (13): 1327–35

49. Futier E, Constantin JM, Combaret L, Mosoni L, Roszyk L, Sapin V, et al. Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. Crit Care 2008;12(5):R116.

50. DeRuisseau KC, Shanely RA, Akunuri N, Hamilton MT, Van Gammeren D, Zergeroglu AM, et al. Diaphragm unloading via controlled mechanical ventilation alters the gene

expression profile. Am J Respir Crit Care Med 2005; 172(10): 1267-75.

51. Kondo H, Nakagaki I, Sasaki S, Hori S, Itokawa Y. Mechanism of oxidative stress in skeletal muscle atrophied by immobilization. Am J Physiol 1993; 265(6 Pt 1):E839-44.

52. Jubran A. Critical illness and mechanical ventilation: effects on the diaphragm. Respir Care 2006 ;51(9):1054-64.

53. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Crit Care Med 2011;39(12):2627-30.

54. Supinski GS, Callahan LA. Diaphragm weakness in mechanically ventilated critically ill patients. Crit Care 2013;17(3):R120.

55. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G. Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care 2010;14(4):R127.

56. Mendez-Tellez PA, Needham DM. Early physical rehabilitation in the ICU and ventilator liberation. Respir Care 2012;57(10):1663-9.