# A Study of Diaphragmatic Ultrasound in Critically Ill Patients with Therapeutic Theophylline Trials

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**Abstract**

**Background and Aim:** This study assessed the response of critically ill patients with diaphragmatic dysfunction to theophylline treatment and the impact of diaphragmatic function on hospital stay and mortality.

**Patients and Methods:** An interventional, randomized controlled trial that included 46 patients with diaphragmatic dysfunction was divided randomly into two groups: the study group received theophylline, and the control group received only their usual medications. All patients in this study were subjected to medical history taking, physical examination, laboratory investigations, and diaphragmatic US before and after theophylline treatment.

**Results**: In the study group, there was a significant increase in each thickening fraction (16.95 ± 1.49 vs. 23.69 ± 7.21 (%); $p < 0.001$) and excursion (8.65 ± 1.13 vs. 13.32 ± 4.15 (mm); $p < 0.001$). Study group patients had significantly shorter ICU stays (10.17 ± 4.15 vs. 14.34 ± 7.04 (days); $p= 0.01$). Survivors had significantly higher baseline thickening fraction (17.47 ± 1.12 vs. 16.04 ± 1.87 (%); $p < 0.001$) and excursion (8.85 ± 1.10 vs. 7.70 ± 1.60 (mm); $p < 0.001$) in comparison to patients who died. Diaphragmatic function can accurately predict mortality in critically ill patients at cutoff point < 12.5%, thickening fraction, and at cutoff point < 8 mm, excursion with an overall accuracy of 70.6% and 74.1%, respectively.

**Conclusion**: Theophylline in critically ill patients was shown to improve diaphragmatic function and has favorable outcomes such as decreased duration of ICU stay. Diaphragmatic thickening fraction and excursion can be used as a predictor tool of mortality in the ICU.

**Keywords:** Diaphragmatic dysfunction, diaphragmatic thickening fraction, diaphragmatic excursion, theophylline.

## Introduction

Critically ill patients are patients who require particular requirements while in the hospital. Since most of them are mechanically ventilated, it is crucial to continuously monitor vital signs, including the respiratory muscles, particularly the diaphragm, which is surprisingly not a routine procedure in Intensive Care Units **[1]**.

Even after a brief duration of hospitalization, critical illness myopathy,

polyneuropathy, and mechanical ventilation are frequently the cause of diaphragmatic dysfunction in ICU patients **[2]**.

## Patients and Methods:

### Study Setting and Design:

This interventional, randomized controlled trial study was conducted in the Critical Care Unit, Assiut University, from Jan. 2020 to June 2022.

### Participants:

The study targeted patients that are mechanically ventilated with diaphragmatic dysfunction with a total number of 46 cases; sample size was calculated using OpenEpi, Version 3, with CI 95%, power of the study 80%, and based on variations in the baseline diaphragmatic excursion (DE) of both hemidiaphragms between groups, **Table (1) [3]**.

The sample size was divided into two groups, 23 patients in each group. The study group received theophylline for 10 days during a hospital stay, while the control group received only their usual treatment.

### Inclusion Criteria:

1- Age > 18 years old.

Critical ill patients (mechanically ventilated) were admitted to our ICU with diaphragmatic dysfunction, defined using US examination as diaphragmatic excursion < 10 mm and diaphragmatic thickening fraction <20%.

### Exclusion Criteria:

1. Pneumothorax or ascites presence.
2. Previous thoracic surgery or neuromuscular disease.
3. Poor image quality.
4. Congenital diaphragmatic hernia.
5. A history of diaphragmatic paralysis, cervical spine trauma, or neuromuscular disorders.
6. Pneumomediastinum.
7. Significant pleural effusion.
8. Intra-abdominal hypertension.
9. Uncontrolled arrhythmia or seizure.

### Ethics Approval and Consent to Participate:

The appropriate ethical committee of the Faculty of Medicine, Assiut University, approves the study. Informed consent was obtained from participants to participate in the study.IRB:17100959, Date:10-02-2020.

### Methodology:

All patients included in this study were subjected to the following:

- Full medical history.
- Full clinical examination, especially vital signs (blood pressure, heart rate, respiratory rate, temperature, GCS).
- Laboratory investigation: 1. Complete blood count (CBC). 2. Serum sodium and potassium. 3. Urea and creatinine levels. 4. ABG.
- ECG.
- APACHE II score calculation.
- Assessment of diaphragmatic function (before theophylline treatment): At the patient's bedside, transthoracic ultrasonography was done with a SonoScape E2 Pro machine (SonoScape Medical Inc.) by a skilled intensivist. Both the B- and anatomical M-modes were used to conduct the examination. Patients were examined while they were in the supine position. Three consecutive tidal breaths were recorded to obtain diaphragmatic ultrasonography readings, and their averages were used for analysis. Each hemidiaphragm

inspiratory excursion (measured in M-mode during quiet breathing with a 1- to 5-MHz ultrasound transducer). An intercostal or subcostal approach was used to obtain the measurement at the mid-clavicular line. The probe was positioned in the plane where the ultrasound beam perpendicularly crossed the posterior third of the corresponding hemidiaphragm. The point of maximal height of inspiration in the M-mode tracing was used to estimate the amplitude of the diaphragmatic inspiratory excursion. Using a 6–13 ultrasonic transducer in M-mode, diaphragmatic thickening was recorded at the point of apposition during both endpoint inspiration and endpoint expiration. The formula used to compute the diaphragm thickening fraction (TFdi) was (DT at ending inspiration - DT at ending expiration)/ (DT at end-expiration) × 100. The patient care staff was not informed of these results throughout the trial. A pulmonary consultant assessed the picture quality of each image.

- Treatment of the study group patients: 23 received theophylline orally at 300 mg/day for 10 days.
- Follow-up: The diaphragmatic US was repeated to both control and study groups using the same technique mentioned above by the same operator, who wasn't informed which group of patients received theophylline and which did not.

Data on diaphragmatic excursion, diaphragmatic thickening fraction, length of ventilatory support, ICU stay, and mortality were collected.

**Analytical Statistics:**

SPSS (Statistical Package for the Social Science, version 20, IBM, Armonk, New York) was used to gather and analyze the data. The student t-test was used to compare quantitative data presented as mean ± standard deviation (SD). Number (n) and percentage (%) represent nominal data. The Chi2 test was applied to these data. Logistic regression analysis was used in the current study to assess the mortality predictors. The accuracy of chest ultrasound findings for predicting mortality in the studied patients was assessed using a receiver operating characteristic (ROC) curve. A 95% confidence level was used, so a P-value was considered significant if it was less than 0.05. The confidence level was 95%; therefore, the P-value was deemed significant if < 0.05.

**Results:**

Table (2) shows both groups had insignificant variations regarding baseline thickening fraction (16.95 ± 1.49 vs. 16.43 ± 1.91 (%); p= 0.30) and excursion (8.65 ± 1.13 vs. 7.60 ± 1.52 (mm); p= 0.06) but during follow up the study group had significantly higher thickening fraction (23.69 ± 7.21 vs. 15.67 ± 2.87 (%); P < 0.001) and excursion (13.32 ± 4.15 vs. 8.01 ± 2.22 (mm); P < 0.001) After theophylline therapy; in the study group, there was significant increase in each of thickening fraction (16.95 ± 1.49 (before theophylline) vs. 23.69 ± 7.21 (%) (after theophylline); P < 0.001) and excursion (8.65 ± 1.13 (before theophylline) vs. 13.32 ± 4.15 (mm) (after theophylline); p 0.05).

Table (3) shows that patients in the study group had significantly shorter duration of ICU stay (10.17 ± 4.15 vs. 14.34 ± 7.04 (days); p= 0.01). Both groups had insignificant differences as regards frequency of ventilatory support

(43.5% vs. 30.4%; p= 0.27) and ventilation duration (6.27 ± 3.60 vs. 7.73 ± 2.65 days; p= 0.18).

It was found that patients who died had significantly higher frequency of diabetes mellitus (64% vs. 23.8%; p= 0.007) and mean APACHE-II (23.76 ± 7.90 vs. 17.33 ± 6.08; P < 0.001) in comparison to surviving patients. Other data showed no significant differences between both groups, illustrated in **Table (4)**.

Surviving patients had significantly higher baseline thickening fraction (17.47 ± 1.12 vs. 16.04 ± 1.87 (%); P < 0.001) and excursion (8.85 ± 1.10 vs. 7.70 ± 1.60 (mm); P < 0.001) in comparison to passed away patients; illustrated in **Table (5)**.

Based on the current study, predictors of mortality among the studied patients were diabetes mellitus with odd's ratio (OR) was 1.98, APACHE-II with OR was 2.90, baseline thickening fraction with OR was 3.11, and excursion with OR was 3.20, **Table (6)**.

At cutoff point > 21, the APACHE-II score had 72.1% accuracy for mortality prediction among the studied patients with area under the curve (AUC) of 0.72. At a cutoff point < 12.5%, the thickening fraction had 70.6% accuracy for mortality prediction among the studied patients with AUC, which was 0.71. At a cutoff point < 8 mm, excursion had 74.1% accuracy for predicting mortality among the studied patients, and AUC was 0.75, **Table (7) Figure (1)**.

**Tables:**

**Table (1):** Sample size for comparing two means

| **Input data** | | | |
|---|---|---|---|
| Confidence interval (2 sided) | 95% | | |
| Power | 80% | | |
| Ratio of sample size (Group 2/ Group 1) | 1 | | |
| | **Group 1** | **Group 2** | **Difference*** |
| Mean | 6.9 | 0.5 | 6.4 |
| Standard deviation | 9.1 | 5.7 | |
| Variance | 82.1 | 32.49 | |
| Sample size of Group 1 | 23 | | |
| Sample size of Group 2 | 23 | | |
| Total sample size | 46 | | |

**Table (2):** Diaphragmatic function among the studied groups

| | **Study group (n= 23)** | **Control group (n= 23)** | ***P-value*** |
|---|---|---|---|
| **Thickening fraction (%)** | | | |
| Baseline | 16.95 ± 1.49 | 16.43 ± 1.91 | 0.30 |
| Follow up | 23.69 ± 7.21 | 15.67 ± 2.87 | **< 0.001** |
| ***P*2 value** | **< 0.001** | 0.10 | |
| **Excursion (mm)** | | | |
| Baseline | 8.65 ± 1.13 | 7.60 ± 1.52 | 0.06 |
| Follow up | 13.32 ± 4.15 | 8.01 ± 2.22 | **< 0.001** |
| ***P*2 value** | **< 0.001** | 0.29 | |

**Table (3):** Outcome and hospital stay among the studied groups

| | **Study group (n= 23)** | **Control group (n= 23)** | ***P-value*** |
|---|---|---|---|
| ICU stay (day) | 10.17 ± 4.15 | 14.34 ± 7.04 | **0.01** |
| Mechanical ventilation | 10 (43.5%) | 7 (30.4%) | 0.27 |
| Duration of ventilation (day) | 6.27 ± 3.60 | 7.73 ± 2.65 | 0.18 |
| Outcome | | | 0.50 |
| Alive | 11 (47.8%) | 10 (43.5%) | |
| Died | 12 (52.2%) | 13 (56.5%) | |

Data expressed as frequency (percentage) mean (SD). *P-value* was significant if < 0.05.

**ICU**: Intensive Care Unit

**Table (4):** Characteristics of the studied patients based on the outcome

| | **Outcome** | | ***P-value*** |
|---|---|---|---|
| | **Alive (n= 21)** | **Died (n= 25)** | |
| Age (years) | 54.19 ± 17.51 | 60.92 ± 11.41 | 0.12 |
| Sex | | | |
| Male | 14 (66.7%) | 13 (52%) | 0.24 |
| Female | 7 (33.3%) | 12 (48%) | |
| Comorbidities | | | |
| Diabetes mellitus | 5 (23.8%) | 16 (64%) | **0.007** |
| Hypertension | 4 (19%) | 10 (40%) | 0.11 |
| Ischemic heart disease | 5 (23.8%) | 5 (20%) | 0.51 |
| Chronic kidney disease | 5 (23.8%) | 7 (28%) | 0.50 |
| Others | 7 (33.3%) | 11 (44%) | 0.33 |
| Causes of admission | | | |
| Pneumonia | 13 (61.9%) | 12 (48%) | |
| Aspiration pneumonia | 1 (4.8%) | 5 (20%) | |
| CHF | 3 (14.3%) | 2 (8%) | 0.47 |
| Sepsis | 2 (9.5%) | 2 (8%) | |
| Hematemesis | 1 (4.8%) | 1 (4%) | |
| Lupus cerebritis | 0 | 2 (8%) | |
| SBP | 0 | 1 (4%) | |
| GCS | 14.42 ± 1.24 | 13.92 ± 2.15 | 0.13 |
| Heart rate (b/m) | 107.76 ± 19.59 | 114.56 ± 15.80 | 0.32 |
| Respiratory rate (c/m) | 29.42 ± 4.93 | 32.12 ± 5.12 | 0.07 |
| MAP (mmHg) | 74.33 ± 21.55 | 69.34 ± 24.67 | 0.47 |
| $pH^+$ | 7.36 ± 0.13 | 7.35 ± 0.13 | 0.89 |
| Leucocytes ($10^3$/ul) | 13.83 ± 6.97 | 15.58 ± 9.93 | 0.49 |
| Hematocrit value (%) | 31.97 ± 5.64 | 28.38 ± 7.12 | 0.06 |
| Potassium (mg/dl) | 4.20 ± 0.77 | 4.20 ± 0.90 | 0.72 |
| Sodium (mmol/l) | 134.97 ± 6.77 | 133.64 ± 11.51 | 0.98 |
| Creatinine (mmol/l) | 208.87 ± 196.45 | 319.87 ± 224.56 | 0.08 |
| APACHE-II | 17.33 ± 6.08 | 23.76 ± 7.90 | **< 0.001** |

Data expressed as frequency (percentage) mean (SD). P-value was significant if < 0.05.

SBP: spontaneous bacterial peritonitis; GCS: glasgow coma scale; MAP: mean arterial pressure; APACHE-II: acute physiology and chronic health evaluation-II

**Table (5):** Baseline diaphragmatic function in studied patients based on the outcome

| | **Outcome** | | ***P-value*** |
|---|---|---|---|
| | **Alive (n= 21)** | **Died (n= 25)** | |
| Thickening fraction (%) | 17.47 ± 1.12 | 15.04 ± 1.87 | **< 0.001** |
| Excursion (mm) | 8.85 ± 1.10 | 7.70 ± 1.60 | **< 0.001** |

Data expressed as mean (SD). *P-value* was significant if < 0.05.

**Table (6):** Predictors for mortality among the studied patients

| **Variables** | **Odd's ratio** | **95%CI** | ***P-value*** |
|---|---|---|---|
| Diabetes mellitus | 1.98 | 1.22-3.01 | 0.01 |
| APACHE-II | 2.90 | 2.11-5.87 | < 0.001 |
| Thickening fraction | 3.11 | 1.90-4.90 | < 0.001 |
| Excursion | 3.20 | 2.01-5.10 | < 0.001 |

P-value was significant if < 0.05. CI: confidence interval; APACHE-II: acute physiology and chronic health evaluation-II

**Table (7):** Diaphragmatic function and APACHE-II in the prediction of mortality

| | **APACHE-II** | **Thickening fraction** | **Excursion** |
|---|---|---|---|
| Sensitivity | 68% | 67% | 70% |
| Specificity | 77% | 75% | 79% |
| PPV | 78% | 76% | 80% |
| NPV | 66.7% | 65% | 69% |
| Accuracy | 72.1% | 70.6% | 74.1% |
| Cutoff point | > 21 | < 12.5 | < 8 |
| AUC | 0.72 | 0.71 | 0.75 |
| *P-value* | **< 0.001** | **< 0.001** | **< 0.001** |

P-value was significant if < 0.05. APACHE-II: acute physiology and chronic health evaluation-II; PPV: positive predictive value; NPV: negative predictive value; AUC: area under curve

## Figures

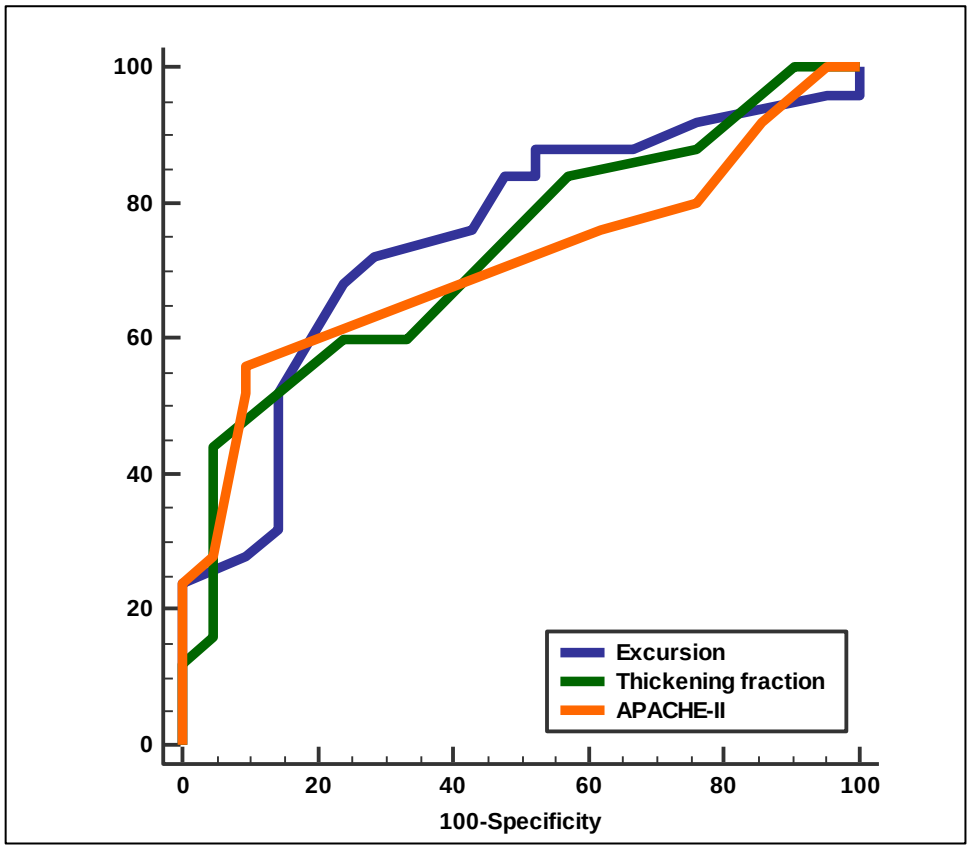


**Figure (1): Diaphragmatic function and APACHE-II in the prediction of mortality**

## Discussion

For critically ill patients, invasive mechanical ventilation is a life-preserving method to offload excessive respiratory muscle effort and produce appropriate pulmonary gas exchange**[4]**.

2008 witnessed the identification of VIDD as a condition affecting critically ill patients **[5]**.

Theophylline has been shown to enhance the contraction of respiratory muscles, including the diaphragm and intercostal muscles **[6-8]**.

According to previous research, diaphragmatic weakening caused by ventilators is common and can even cause injury on the initial day of ventilatory support. Furthermore, the length of mechanical ventilation is substantially connected to the amount of diaphragmatic damage and atrophy **[3, 9]**.

Research on animals has demonstrated that after extended mechanical ventilation, the diaphragm exhibits much higher levels of xanthine oxidase and nicotinamide adenine dinucleotide phosphate oxidase, which produce reactive oxygen species. Because theophylline suppresses xanthine oxidase activity, it potentially protects the diaphragm from contractile failure and oxidative stress brought on by mechanical ventilation **[10, 11]**.

This research has found that theophylline group significantly improved diaphragmatic function during follow-up, as assessed by chest US in the form of thickening fraction and excursion. Similarly, a previous study stated that theophylline enhanced diaphragmatic contraction, and compared to normal diaphragms, theophylline's inotropic action was more pronounced in diaphragms with VIDD **[3]**.

Also, theophylline administration dramatically improved respiratory muscle performance, regarding improved maximal inspiratory pressure and rapid shallow breathing index, in patients with extended ventilation duration **[8]**. Theophylline has been shown in numerous studies to have positive effects on human respiratory muscle function, and it is frequently used in patients who are weaning off mechanical ventilation **[12]**.

A previous study found that in patients who met the requirements for an SBT, needed mechanical ventilation for at least 72 hours, and had ultrasonography evidence of VIDD, low-dose (median, 200 mg/d) theophylline administration substantially enhanced the diaphragmatic contraction **[3]**.

In the current study, it was found that deceased patients had a substantially greater frequency of diabetes mellitus and mean APACHE-II score in comparison to surviving patients. Moreover, based on this study, dying patients had significantly lower baseline diaphragmatic thickening fraction and diaphragmatic excursion than surviving patients.

***Demoule et al. (2013)***[13] demonstrated a correlation between mortality and diaphragm dysfunction in patients with sepsis, indicating that diaphragmatic dysfunction might linked to bad prognosis in those patients **[13]**.

Additionally, ***Supinski and Callahan (2013)***[14] revealed a correlation between mortality and diaphragmatic dysfunction **[14]**. Diaphragmatic dysfunction was observed to occur at a similar rate of 29% in a prospective trial, and it was

related to greater reintubation rates. Nevertheless, this outcome is influenced by the significantly elevated weaning failure rate (59%) and lack of US operators blinding **[2]**.

In the present study, the US operators were not participating in extubation or reintubation decisions. We found that predictors of mortality among the studied patients were diabetes mellitus, APACHE-II score, baseline thickening fraction, and excursion. At the cutoff point < 12.5%, the thickening fraction had 70.6% accuracy for predicting mortality among the studied patients. At cutoff point < 8 mm, excursion had 74.1% accuracy for predicting mortality among the studied patients.

***Saccheri et al. (2020)*** **[15]** found that individuals without diaphragmatic dysfunction and ICU-acquired weakness at the time of mechanical ventilation release had a considerably higher 2-year survival rate than patients with both comorbidities **[15]**.

Meanwhile, weakness acquired in the intensive care unit seemed to have a considerably greater impact on survival than diaphragm dysfunction **[15]**.

Patients with diaphragm dysfunction had greater hospital mortality rates than patients without diaphragm dysfunction, which appears to be comparable to the poor predictive value of cardiac dysfunction brought on by sepsis **[16, 17]**.

This result also aligns with the poor prognostic significance of early muscle mitochondrial dysfunction and aberrant nerve conduction in sepsis patients. It is yet unknown if there is a causal relationship between diaphragmatic dysfunction and mortality **[18, 19]**.

Our findings are consistent with a recent study that suggests that diaphragm function plays a crucial role in determining the outcome of the weaning trial but that after patients are weaned off the ventilator, other risk factors—most notably ICU-acquired weakness—largely determine their long-term prognosis **[20]**.

On the other hand, it may come as a surprise that early diaphragm dysfunction did not appear to be linked to longer periods of mechanical ventilation or ICU and hospital stays, given that late-stage critical illness polyneuropathy and myopathy during the ICU stay are linked to challenging weaning and extended mechanical ventilation **[2, 21]**.

Although many previous research reported the efficacy of diaphragmatic thickening fraction and diaphragmatic excursion in predicting weaning outcomes [22-25], no previous study reported these parameters' efficacy in predicting mortality in critically ill patients. This topic was covered in the current study and is its primary area of strength. The primary constraints of the present investigation were the comparatively small sample size, single-center research, and lack of long-term patient follow-up to evaluate the impact of diaphragmatic dysfunction on survival analysis.

## Conclusion

The study results concluded that theophylline treatment in critically ill patients with diaphragmatic dysfunction had been shown to improve diaphragmatic excursion and thickening fraction, has favorable outcomes such as decreased duration of ICU stay, and diaphragmatic thickening fraction and excursion can be used as a predictor tool of mortality in critically ill patients.

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