Use of Ultrasound to Assess Diaphragmatic Thickness as a Weaning Parameter in Invasively Ventilated Chronic Obstructive Pulmonary Disease Patients

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Abstract: Introduction: Predictive indices of weaning from mechanical ventilation are often inaccurate. Despite of the existence of many weaning protocols, often making a correct decision is difficult because the diaphragmatic function is not included in any of the weaning criteria. **Objective:** The aim of this study was to determine the value of diaphragmatic thickness fraction (DTF) measured by B- mode ultrasound as a predictor tool in weaning of invasively ventilated chronic obstructive pulmonary disease patients. **Methods:** A prospective observational study was conducted on 112 invasively ventilated patients with COPD. Demographic, clinical data and laboratory investigations were obtained on admission. Patients underwent a spontaneous breathing trial (SBT) after the reversal of the underlying cause for respiratory failure and when they met all the weaning criteria. Then Rapid shallow breathing index (RSBI) was performed. As RSBI < 105, weaning process was continued for 30 to 120 minutes. During the trial, diaphragm was visualized in the zone of apposition on both sides using a 10-MHz linear ultrasound probe. Diaphragm thickness was recorded at end of inspiration and end of expiration, and the DTF was calculated. Weaning failure was defined as the inability to sustain spontaneous breathing without any form of ventilatory support, for at least 48 h. **Results:** DTF differed significantly between patients who succeeded weaning from mechanical ventilation and those who failed. A cutoff value >29% on the right side and a cut off value >24% on the left were associated with a successful weaning from mechanical ventilation with a 97%sensitivity, 73% specificity, 0.90 positive predictive value (PPV), 0.91 negative predictive value (NPV) and 91% accuracy on both sides. Confidence interval was calculated, and ranged from 0.872- 0.973 for the right side and 0.805- 0.933 for the left side. **Conclusion:** Diaphragmatic thickness fraction detected by B-mode ultrasonography, is associated with high sensitivity, specificity, positive and negative predictive values to determine weaning outcome, in this cohort of COPD.

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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD), the fourth leading cause of death in the world represents an important public health challenge that can be prevented and treated. (WHO, COPD 2000) COPD is a major cause of chronic morbidity and mortality throughout the world. The burden of COPD is projected to increase globally in coming decades because of continued exposure to COPD risk factors and aging of the population. (Lopez, 2006).

Inspiratory muscle weakness in patients with COPD is of major clinical relevance. (Uriona, 2005) Traditionally, inspiratory muscle weakness has been ascribed to hyperinflation induced diaphragm shortening. (Gray-Donald, 1996) However, recently invasive evaluation of diaphragm contractile function, structure, and biochemistry demonstrated that cellular and molecular alterations occur. Most are considered to have pathologic nature that leads to loss of force generating capacity of diaphragm fibers in patients with COPD. (Stubbings, 2008).

Weaning procedures are usually started only after the underlying disease process that necessitated mechanical ventilation has significantly improved or resolved. The patient should also have an adequate gas exchange, appropriate neurological and muscular status, and hemodynamic stability. Weaning from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. The most influential determinant of mechanical ventilator dependency in these patients is the balance between the respiratory load and the capacity of the respiratory muscles to cope with this load. (Esteban, 2000)Weaning indices are objective criteria that are used to predict the readiness of patients to maintain spontaneous ventilation. Predictive indices of weaning from mechanical ventilation are often inaccurate. Despite of the existence of many weaning protocols, often making a correct decision is difficult because the diaphragmatic function is not included in any of the weaning criteria. (Conti, 2004)

Bedside ultrasonography is a valuable tool in the management of intensive care unit patients. It is a non-invasive, safe and easy to use bedside modality that overcomes many of the standard limitations of imaging techniques. (Bushberg, 2012) Bedsides onographic evaluation of the motion of the diaphragm dome has shown to be useful in predicting extubation outcomes; however, factors such as tidal volume, proximity of rib cage and abdominal organs may affect diaphragm motion. (Gerscovich 2001, Jiang 2004 and Kim 2011) Recently it has been suggested that ultrasound measurements of diaphragm muscle thickening in inspiration during weaning could provide an estimation of extubation success. Using ultrasound in measuring the percentage variation of diaphragm thickness (tdi) between end-inspiration and end-expiration (Δtdi%), has become a valuable tool in the management of intensive care unit patients. This non-invasive, low-cost and fast to perform technique seems to predict with a good accuracy the extubation failure. (Zanforlin, 2014)

2. Material and Methods

Patients

The study was carried out on 112 COPD patients who were invasively mechanically ventilated and were admitted to the department of Critical Care Medicine in the Alexandria Main University Hospital.

The Approval of the Medical Ethics Committee of Alexandria faculty of Medicine was taken. An informed consent from the patients' next of kin was obtained before conducting the study.

Inclusion criteria:

1. COPD patients who were invasively mechanically ventilated.
2. ≥18 years.
3. Fulfilling weaning criteria: (Cook, 2000 and MacIntyre, 2001)

- Evidence for some reversal of the underlying cause for respiratory failure.
- Adequate oxygenation; PaO_2/FIO_2 ratio ≥ 150, $FI0_2 \leq 0.40$, $Sp0_2 \geq 90\%$, $PaO_2 \geq 60$ and PEEP ≤ 8 cmH20.
- PH ≥ 7.30.
- MIP < -20 to -30 cmH2O.
- Respiratory rate ≤ 35 bpm.
- Heart rate ≤ 140 bpm.
- SBP 90 – 180 mmHg.
- Hemodynamic stability; no or minimal vasopressors or inotropes.
- Appropriate level of consciousness, No continuous sedation infusion nor neuromuscular blocking agents.
- Afebrile.
- Adequate hemoglobin ≥8 g/dl and/or no evidence of hemorrhage.

Exclusion criteria:

1. History of diaphragmatic or neuromuscular disease.
2. Morbidly obese patients (BMI > 40).
3. Not meeting the weaning criteria above.

All selected patients were subjected to the following:

1- Complete history taking.

2- Clinical examination:

- General and Chest examination.
- Vital sign (heart rate, respiratory rate, mean arterial blood pressure, temperature).

3- Laboratory evaluation:

- Arterial blood gases (on admission, before Spontaneous Breathing Trial (SBT))
- Routine investigation: (Complete blood count (CBC), Sodium (Na), Potassium (K), Urea, Creatinine, Liver enzymes, Coagulation profile).

4- Radiologically:

- X-Ray chest done on admission and before weaning.
- CT chest done when needed

This study was scheduled as Follow:

5- Evidence for reversal of the underlying cause for respiratory failure.

6- Check fulfilling weaning criteria as mentioned above.

7- The weaning process was explained to the patient.

8- Spontaneous Breathing Trial (SBT) was done by placing patients on pressure support 5 cmH20 and CPAP 5 cmH20. Then Rapid shallow breathing index (RSBI) was performed. As RSBI < 105, weaning process was continued for 30 to 120 minutes.

9- Diaphragmatic thickness was measured on both sides during the SBT and diaphragmatic thickness fraction was calculated as follow: (Thickness at end inspiration − Thickness at end expiration/ Thickness at end expiration.)

10- The SBT was considered successful when the patient succeed to pass from 30 to 120 minutes without the appearance of any of the following termination criteria:

- Respiratory rate> 35 bpm.
- Blood pressure changing as:
  - A drop of 20 mm Hg systolic or.
  - A rise of 30 mm Hg systolic or.
  - Systolic value > 180 mm Hg or.
  - A change of 10mm Hg diastolic.
- Heart rate increasing > 20% or exceeds 140 bpm.

- New arrhythmias.
- Increase work of breathing.
- Patient agitation or anxiety.
- Sp02 < 90% with increasing FI02 ≥ 50.
- Deterioration of arterial blood gas values.

Technical Aspects of Measuring Diaphragm Thickness:

- Mindray digital ultrasonic diagnostic imaging system, model DP- 20 used and real time movement of the diaphragm was recorded by B-mode using a 10 MHz linear transducer.
- Subjects were in the supine position.
- The probe was placed in the 8th or 9th intercostal space in the mid axillary or anterior axillary line.
- The probe was positioned perpendicular to the chest wall in a long axis configuration with the left end cephalad. The probe position was adjusted until the diaphragm could be clearly visualized.
- The diaphragm is identified as the last set of parallel lines on the image, corresponding to the pleural and peritoneal membranes overlying the less echogenic muscle.
- Once identified, real time movement of the diaphragm was recorded on B-mode ultrasonography.
- End expiratory diaphragm thickness was measured in three consecutive respiratory cycles during the end expiratory pause, when the diaphragm is relaxed. And End inspiratory diaphragm thickness was measured in three consecutive respiratory cycles during the end inpiratory pause.
- Measurements were made from the middle of the pleural line to the middle of the peritoneal line.
- The DTF was calculated as percentage from the following formula: Thickness at end inspiration − Thickness at end expiration /Thickness at end expiration.
- All subjects in which image acquisition failed were excluded from the study.

Outcome:

1- Successful weaning

2- Weaning failure: This is defined as the inability to sustain spontaneous breathing for at least 48 hours without any ventilatory support.

Statistical analysis of the data

Data analyses were performed using IBM SPSS software package version 20.0. (Kirkpatrick, 2013) Qualitative data were described using number and percent. 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 Firsher's Exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using 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. Quantitative data were described using mean and standard deviation for normally distributed data while abnormally distributed data was expressed using median, minimum and maximum. For normally distributed data, comparisons between two groups were done using independent t-test while for abnormally distributed data, Mann-Whitney Test was used. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for ultrasound derived measurements of diaphragmatic thickness fraction (Δtdi %) in both sides. Receiver operating characteristic (ROC) curves were used to evaluate the efficacy of ultrasound derived measurements of diaphragmatic thickness fraction in predicting extubation success or failure. A p value < 0.05 was considered statistically significant.

Results

During the study period one hundred and twelve mechanically ventilated COPD patients were studied. 82 patients were successfully weaned from mechanical ventilation while the remaining 30 patients failed. Table 1 show the demographic data and characteristics of the both groups included in the study. There were statistically significant differences between the groups in terms of Hb, platelets and potassium being less in failure group while serum creatinine and urea were higher in it. As regards ABG on admission, there was a significant difference between both groups in terms of $PaCO_2$, HCO_3 and PaO_2 being less in failure group too.

Table2 shows comparison between the two groups regarding weaning criteria. The difference between proposed weaning indices in the current study was not significant between both groups except for MIP and Hb which were less in the failure group while RSBI and PEEP were higher in that group.

Diaphragm thickness fraction Δtdi % differed significantly between patients who succeeded weaning from mechanical ventilation and those who failed as shown in table 3. A ROC curve was used to assess the diagnostic accuracy of Δtdi % in predicting weaning outcome. A cutoff value >29% on the right side and a cut off value >24% on the left were associated with a successful weaning from mechanical ventilation with a97%sensitivity, 73% specificity, 0.90 PPV, 0.91 NPV and 91% accuracy on both sides. The area under the ROC curve for Δtdi% on the right and left side was 0.928 and 0.877 respectively (figure1, 2). Confidence interval was calculated, and ranged from 0.872- 0.973 for the right side and 0.805- 0.933 for the left side as shown in table 3.

The diaphragmatic thickness (tdi) and Δtdi% values for both groups are shown in table 4 and 5. Of the 82 patients who were successfully extubated, 81 had a right side Δtdi% of ≥29% and of the 30 who failed extubation, 18 had a right side Δtdi% < 29%. While on the left side, 80 patients out of the 82 patients who were successfully extubated had a Δtdi% of ≥24% and 20 patients out of the 30 who failed extubation had a Δtdi% < 24%. Twelve patients failed weaning despite having a right side Δtdi% ≥29%. However, factors unrelated to diaphragm contractility such as the development of fluid overload, fever and mucous plugging precipitated respiratory failure and the need for ventilation. These non-mechanical factors lowered the NPV and specificity of Δtdi%. The remaining 18patients who failed extubation had a right side Δtdi% < 29% and weaning failure was attributed to ‘Respiratory pump 'failure.

Table (1): Baseline characteristics of patients in success and failure groups on admission.

	Baseline characteristic data for all patients	Weaning		Test of sig.	*P*
		Successful (n = 82)	Failed (n = 30)		
Age (years)	42.0 – 85.0 (62.61 ± 12.04)	62.41 ± 12.99	63.13 ± 9.13	t=0.327	0.745
Gender					
Male	86.6%	74 (90.2%)	23 (76.7%)	χ^2=3.491	^{FE}P=0.113
Female	13.4%	8 (9.8%)	7 (23.3%)		
Vital signs					
HR (bpm)	97.71 ± 14.89	95.20 ± 14.94	104.40 ± 12.72	t=0.327	0.745
MAP (mmHg)	90.72 ± 22.15	91.55 ± 23.93	88.47 ± 16.48	t=0.770	0.444
Temperature (°C)	37.75 ± 0.39	37.73 ± 0.35	37.80 ± 0.48	t=0.856	0.394
RR (breath/min)	36.04 ± 6.63	35.46 ± 7.22	37.60 ± 4.39	t=1.889	0.062
GCS					
On admission	13.55 ± 2.01	13.61 ± 1.91	13.40 ± 2.28	0.352	0.725
ABG on admission					
pH	7.20 ± 0.08	7.21 ± 0.06	7.18 ± 0.12	t=1.054	0.299
$PaCO_2$ (mmHg)	79.33 ± 21.58	82.45 ± 22.73	70.80 ± 15.35	t=3.096*	0.003*
PO_2 (mmHg)	83.25 ± 39.20	88.20 ± 37.65	69.73 ± 40.78	Z=2.885*	0.004*
HCO_3(meq/l)	30.49 ± 9.69	32.11 ± 9.84	26.05 ± 7.82	t=3.039*	0.003*
SaO_2 (%)	0.88 ± 0.08	0.90 ± 0.06	0.83 ± 0.10	t=3.978*	<0.001*
Lab. investigations					
Na (mEq/L)	136.74 ± 5.07	136.26 ± 5.39	138.07 ± 3.84	t=1.969	0.053
K (mEq/L)	4.39±0.75	4.70 ± 0.58	3.52 ± 0.43	t=10.287*	<0.001*
Hb(g/dl)	12.61 ± 3.31	13.62 ± 3.04	9.83 ± 2.28	Z=6.213*	<0.001*
WBC	16.19 ± 12.30	14.36 ± 4.88	21.18 ± 21.84	Z=1.371	0.170
Platelets	246.21 ± 91.26	256.43 ± 95.10	218.27 ± 74.25	Z=2.236*	0.025*
Creatinine	2.99 ± 3.81	1.89 ± 2.40	6.02 ± 5.15	Z=2.983*	0.003*
Urea	97.46 ± 76.08	79.90 ± 64.0	145.47 ± 86.36	Z=3.628*	<0.001*
SGOT	64.54 ± 98.48	52.65 ± 58.91	97.03 ± 161.04	Z=0.487	0.626
SGPT	82.04 ± 219.05	53.35 ± 137.41	160.43 ± 349.62	Z=0.911	0.362
INR	1.23 ± 0.21	1.24 ± 0.21	1.23 ± 0.21	t=0.139	0.890

HR, heart rate; MAP, mean arterial blood pressure; RR, respiratory rate;SaO_2, arterial oxygen saturation; $PaCO_2$, partial pressure of carbon dioxide ; PaO_2, partial pressure of oxygen; HCO_3, bicarbonate; Na, sodium; K, potassium; Hb, hemoglobin; GCS, Glasgow coma score.

Table (2): Comparison between the two groups according to different weaning parameters

	Baseline characteristic data for all patients	Weaning		Test of sig.	*P*
		Successful (n = 82)	Failed (n = 30)		
Weaning parameters					
FIO_2	0.42 ± 0.08	0.41 ± 0.07	0.43 ± 0.09	t=1.267	0.212
SpO_2	0.96 ± 0.03	0.96 ± 0.02	0.96 ± 0.04	t=0.833	0.410

PaO_2	117.47 ± 57.39	112.60 ± 55.05	130.80 ± 62.37	Z=1.144	0.252
PEEP	5.59 ± 0.75	5.46 ± 0.67	5.93 ± 0.87	t=2.686*	0.010*
PH before weaning	7.43 ± 0.04	7.43 ± 0.06	7.43 ± 0.04	t=0.048	0.962
HI	275.11 ± 103.42	265.49 ± 96.36	301.40 ± 118.44	Z=0.986	0.324
MIP	-63.17 ± 13.54	-67.74 ± 11.50	-50.67 ± 10.56	7.108*	<0.001*
RSBI	69.16 ± 19.68	60.66 ± 13.83	92.37 ± 13.67	10.777*	<0.001*
RR(breath/min)	17.61 ± 3.11	17.20 ± 2.19	18.73 ± 4.66	1.739	0.091
HR(beat/ min)	83.68 ± 8.14	83.0 ± 7.79	85.53 ± 8.90	1.466	0.145
SBP(mm Hg)	124.64 ± 12.73	124.15 ± 11.54	126.0 ± 15.67	0.592	0.557
Hb(g/dl) before weaning	12.16 ± 2.43	12.74 ± 2.33	10.57 ± 1.98	4.542*	<0.001*
Temperature2	37.15 ± 0.17	37.15 ± 0.17	37.15 ± 0.19	0.188	0.852
GCS	14.93 ± 0.25	14.95 ± 0.22	14.87 ± 0.35	1.252	0.218

FIO_2, fraction of inspired oxygen; SaO_2, arterial oxygen saturation PaO_2, partial pressure of oxygen; PEEP, positive end expiratory pressure; HI, hypoxic index; MIP, maximum inspiratory pressure; RSBI, rapid shallow breathing index; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; Hb, hemoglobin; GCS, Glasgow coma score.

Table (3): Agreement (sensitivity, specificity and accuracy) for right DTF to diagnose successful weaning

	Right DTF	Left DTF
AUC	0.928*	0.877
p	<0.001*	<0.001*
Youden index	0.708	0.708
Cutoff	>0.29	>0.24
Sensitivity	97.56	97.56
Specificity	73	73.33
PPV	90.9	90.9
NPV	91.7	91.7
C.I (95.0%)	0.872- 0.973	0.805-0.933
Accuracy	91.07	91.07

DTF, diaphragm thickness fraction; AUC, area under the curve, PPV, positive predictive value; NPV, negative predictive value, CI, confidence interval.

Table (4): Comparison between the two groups according to tdi at end-inspiration and tdi at end-expiration on both sides

		Total (n = 112)	Successful (n = 82)	Failed (n = 30)	t	*p*
tdi at end-inspiration (mm)	**Right**					
	Min. – Max.	3.0 – 7.20	3.10 – 7.0	3.0 – 7.20	0.812	0.418
	Mean ± SD.	4.89 ± 1.0	4.94 ± 0.95	4.76 ± 1.12		
	Median	5.30	5.30	5.20		
	Left					
	Min. – Max.	2.80 - 5.80	2.80 – 5.60	3.0 – 5.80	0.426	0.671
	Mean ± SD.	4.32 ± 0.65	4.34 ± 0.63	4.28 ± 0.70		
	Median	4.50	4.50	4.50		
tdi at end-expiration(mm)	**Right**					
	Min. – Max.	2.10 – 5.70	2.10 – 5.10	2.70 – 5.70	1.274	0.205
	Mean ± SD.	3.61 ± 0.74	3.56 ± 0.72	3.76 ± 0.78		
	Median	3.75	3.60	3.95		
	Left					
	Min. – Max.	2.0 – 4.70	2.0 – 4.20	2.70 – 4.70	2.184*	0.031*
	Mean ± SD.	3.30 ± 0.51	3.24 ± 0.51	3.48 ± 0.50		
	Median	3.40	3.40	3.45		

t: Student t-test, *: Statistically significant at $p \leq 0.05$, tdi, diaphragm thickness.

Table (5): Comparison between the two groups according to DTF on both sides

DTF	Total (n = 112)	Successful (n = 82)	Failed (n = 30)	t	*p*
Right					
Min. – Max.	0.11 – 0.57	0.29 – 0.57	0.11 – 0.39		
Mean ± SD.	0.35 ± 0.09	0.39 ± 0.06	0.26 ± 0.08	8.257*	<0.001*
Median	0.37	0.39	0.27		
Left					
Min. – Max.	0.10 – 0.50	0.22 – 0.50	0.10 – 0.35		
Mean ± SD.	0.31 ± 0.08	0.34 ± 0.05	0.23 ± 0.08	7.623*	<0.001*
Median	0.33	0.34	0.22		

t: Student t-test, *: Statistically significant at $p \leq 0.05$, DTF, diaphragm thickness fraction.

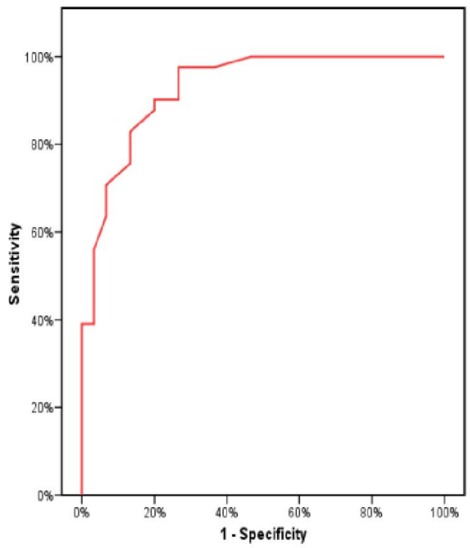

Figure (1): ROC curve for right DTF to diagnose successful weaning

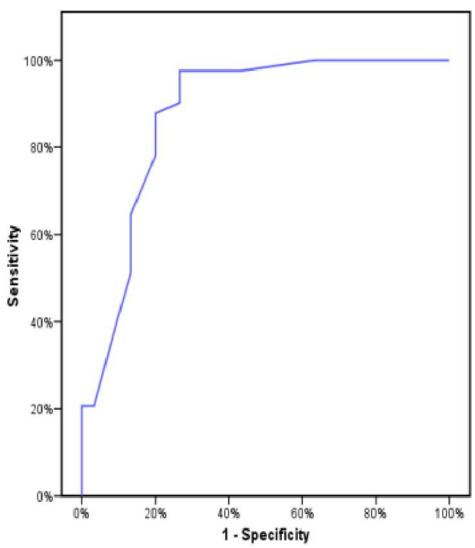

Figure (2): ROC curve for left DTF to diagnose successful weaning

4. Discussion

Ultrasonograghy has become an extension of the physical examination in the clinical practice. Ultrasound is a simple, rapid and non-invasive test that can be repeated several times without radiation hazards. B-mode sonography has been recently proposed as a non-invasive method of quantification of diaphragmatic contractile activity through measurement of diaphragmatic thickness or DTF. (KIM et al, 2011) This technique would be helpful to assess the contribution of the diaphragm to respiratory workload and to predict the extubationfailure. We evaluated a new weaning index consisting in the diaphragm thickening fraction (DTF) assessed by B-mode ultrasound.

In our study population, there were several causes that necessitate invasive ventilation in COPD patients; there was a statistical significance between the studied groups only regarding AKI which was higher in the failure group. That was attributed to many factors; first, patients with AKI often have more comorbidities than those without. Second, fluid overload accompanying AKI development could cause pulmonary edema and impair the patient's respiratory mechanics. (Chao et al, 2013) Our result was consistent with the work of Barakat *et al.* They concluded that the incidence of AKI is relatively high in COPD patients and that Coexisting AKI at exacerbation is prognostic of poor outcome. (Vieira et al, 2007and Barakat et al, 2015)

In the present study there was a significant difference regarding the renal function between the studied groups with higher urea and creatinine in the failed group. In contrary to the current study in which the mean for serum creatinine was 1.89 ± 2.40 and 6.02 ± 5.15 in the success and failure group respectively, Nava *et al.* found no significant difference between the two groups (the mean for serum creatinine was 1.1 ± 0.6 in the success group versus 1.0 ± 0.3 in failure one) in his studies about survival and prediction of successful ventilator weaning in COPD. (Nava et al, 1994)

In the current study, there was a significant difference regarding hemoglobin between the studied groups on admission and before weaning. The failure group was anemic. Lai *et al* .studied the relation between hemoglobin level and weaning outcome from mechanical ventilation in which they concluded that patients whose hemoglobin was >8 g/dL were more likely to be successfully weaned. (Lai et al, 2013) Hemoglobin plays a critical role in oxygen delivery and may affect cardiac and respiratory muscle workload. (Guo et al, 2015)

Platelets count also was found to have a significant difference between success and failure group. Cakmak*et al.* studied platelets as an indicator of inflammation in COPD and found that the platelet count was significantly higher in COPD group than control group and as the severity of the disease increase platelet count also revealed a statistically significant increase. (Cakmak et al, 2009) While Rahimi-Rad et al., found that thrombocytopenia was associated with poor outcome in AECOPD and that thrombocytopenia could be considered as a marker for the assessment of inflammation and prognosis in AECOPD patients. The mild thrombocytopenia present in the failure group in the present study might be explained by the fact that thrombocytopenia might be a marker of bacterial infection and sepsis. (Rahimi-Rad et al, 2015)

Regarding ABG on admission there was a significant difference between the two groups regarding PaCO2 (mean 82.45 ± 22.73 in the success versus 70.80 ± 15.35 in the failure group). Although the $PaCO_2$ in failure group is less than success one this was attributed to the difference in the bicarbonate level which was less in failure group (mean 32.11 ± 9.84 versus 26.05 ± 7.82 in the success and failure group respectively with a p value 0.003). That might be attributed to the fact that respiratory acidosis is not the only acid-base disturbance observed in patients with COPD. The presence of comorbidity and side effects of some drugs used to treat COPD patients cause different disorders. Heart failure, acute pulmonary edema, renal failure and the onset of sepsis or severe hypoxia are the most common causes of metabolic acidosis associated with hypercapnia. (Bruno et al, 2012) This will increase the demand for ventilation through compensatory respiratory alkalosis, further disrupting the relationship between the patient's ventilatory needs and capabilities. In contrary to Nava et al studies, although they found a significant difference in $PaCO_2$ between the studied groups, the failure group had a higher $PaCO_2$ than the success one (mean 52.50± 9.75 in the success versus 68.25 ± 18 in the failure group). (Nava et al, 1994)

As regards (PaO2) on admission, there was a significant difference between the 2 groups (mean 88.20 ± 37.65 and 69.73 ±40.78 in the success and failure group respectively). The failure group found to be more hypoxic on admission and that was consistent with Nava et al studies in which there was a significant difference regarding PaO2. The success group had a mean 51.00 ± 7.50 while the mean for the failed one was 43.50 ± 8.25. (Nava et al, 1994) This might be explained by the increase in prevalence of alveolar hypoxia and hypoxemia as COPD severity increases and that chronic hypoxemia contributes to the development of adverse sequelae of COPD, such as pulmonary hypertension, secondary polycythemia, skeletal muscle dysfunction, and systemic inflammation. (Kent et al, 2011)

Potassium level was found to have a significant difference between the studied groups in the present study (mean 4.7± 0.58 meq/lit versus 3.52 ± 0.43meq/lit in the success and failure group respectively) while there was no significant difference regarding sodium level. Hypokalemia may be attributed to long standing steroid therapy, use of beta 2-adrenoceptor agonists, use of diuretics and malnutrition. Hypokalemia causes muscle weakness and is associated with poor outcome as weaning failure. Das et al assessed the levels of serum sodium and potassium in subjects with acuteepisodes of COPD and their healthy control, they found a significantly low level of serum sodium (133 ± 6.86 meq/lit) and potassium (3.39 ± 0.96 meq/lit)) in subjects with acute exacerbation of COPD than their healthy counterparts (sodium 142 ± 2.28 meq/lit and potassium 4.52 ± 0.02 meq/lit), they concluded that serum sodium and potassium level get deranged in subjects with acute exacerbations of COPD. (Das et al, 2010)

Although the evaluation of the motion of the diaphragm dome has shown to be useful in predicting extubation outcomes, however factors such as tidal volume, proximity of the rib cage and abdominal organs may affect diaphragm motion. (Zanfrolin et al, 2014) Also the acoustic window on the left side is not easily acquired as the spleen window is small. These confounders were circumvented by visualizing the diaphragm muscle itself in the zone of apposition. As the volume of the diaphragm muscle mass is constant, when it contract, it shortens and became thickened and that indicate diaphragm strength. Gottesmanet al found that diaphragm thickening was absent in patients with diaphragm paralysis. Summerhill *et al.* followed patients with phrenic neuropathy and found that patients who did not recover, did not exhibit any thickening. (Guttesman et al, 1997and Summerhill et al, 2008)

In the current study DTF was evaluated as a new predictive index of weaning in COPD. The cut off value of DTF >29% at the right side was associated with successful weaning with 97% sensitivity, 73% specificity, 0.90 positive predictive value (PPV), 0.91 negative predictive value (NPV) and 91% accuracy. DiNino *et al.* have recently investigated using ultrasound measurement of diaphragmatic thickness rather than diaphragm motion to predict extubation outcome in any patient ventilated due to respiratory failure regardless the etiology. They concluded that this method may be especially helpful in reducing the number of failed extubation. The resulting sensitivity and specificity was 88% and 71%, respectively. The PPV of a Δtdi% ≥ 30% for extubation success was 91% and the NPV of a Δtdi< 30% for extubation failure was 63%. (DiNino et al, 2014) Also Ferrari et al evaluates the DTF as a predictive index of weaning after a spontaneous breathing trial by using B-mode ultrasonography to patients on tracheostomy tube after failing one or more attempts of weaning. They concluded that DTF may perform similarly to other weaning indices. They found that a cut off value of DTF >36% was associated with a successful SBT with 82% sensitivity, 88% specificity, ppv 0.92 and Npv 0.75. (Ferrari et al, 2014)This discrepancy between the current study and DiNino and Ferrari studies might be attributed to the difference in the studied population as this study was carried on patients with COPD presenting with respiratory failure. Research on diaphragm ultrasound is constantly evolving with latest study indicating its possible applications also in diseases such as COPD. But studies regarding diaphragmatic thickness in COPD are still few. Baria et al. studied the diaphragm in moderate and severe COPD patients and compared it with healthy control. They aimed at defining the standard values for average diaphragm thickness at end expiration and thickening ratio in COPD using B-mode ultrasound. They found no significant difference in diaphragm thickness or thickening ratio between both healthy control and COPD patients except COPD patients with severe air trapping (residual volume >200%) in which the only difference was that the thickening ratio was higher on the left side. (Baria et al, 2014)

In the current study, we found that diaphragm contractions as assessed by Δtdi% performed better than simultaneous measure of RSBI during SBT. Although all participants had RSBI <105 according to weaning criteria and were eligible for weaning, 30 patients failed. This was consistent with the result of DiNino, who previously explained that RSBI is an integrative function of all inspiratory muscle. So if the diaphragm is failing, the non- diaphragmatic inspiratory muscles will compensate to preserve tidal volume and that will mask the diaphragm weakness initially and as the ribcage muscles are more fatigable and weaker than diaphragm, these muscles will not be able to sustain adequate ventilation. So patients may initially have an acceptable RSBI and still fail. (DiNino et al, 2014). In the present study RSBI had a median of 60 and 100 in success and failure group respectively with a p value <0.001 going with the results of Ferrari *et al.* study in which RSBI had a median 70 in the success group and 120 in the failure group with a p value <0.0001. (Ferrari *et al*, 2014).

MIP is a measure of the strength of inspiratory muscles including the diaphragm, it allows for the assessment of ventilatory failure. In the present study, MIP was found to have a significant difference between the success and failed group although both groups have MIP< -20 to -30 cmH2O according to the weaning criteria previously described. The mean was found to be -67.74 ± 11.50 and -50.67 ± 10.56 in the success and failure group respectively with a p value <0.001. Going with similar results obtained by study of Ferrari *et al.*who found a significant difference in MIP (mean -82.9 ± 13.6 versus -41.2 ± 11.2 in both group respectively with a p value< 0.0001) but his results were not from COPD patient precisely. (Ferrari et al, 2014) Ucar *et al.* studied weaning of COPD patients and found a significant difference in terms of MIP between the success and failed groups (-30 versus -18 cmH2o, p= 0.008). (Ucar *et al*, 2010)

In the present study there was a significant difference only for tdi at end-expiration in the left side. It was found to be more thickened in the failure group than successful group. The clinical significance of this finding is still unclear. On contrary to Ferrari et al studies that found COPD patients with severe air trapping had an increased thickening ratio on the left side, implying an increased ability of the diaphragm to contract on that side.(Ferrari et al, 2014).Although DiNinio studies showed that tdi at end expiration on the right side can predict weaning outcome with he stated that this model failed to improve extubation predictions. He attributed that to the variability of tdi among individuals. Also this supports the idea that measuring the percentage of diaphragm shortening is more indicative of diaphragm function. (DiNino et al, 2014). In this context, Guttesman et al found that tdi alone cannot distinguish between a chronically paralyzed atrophic diaphragm and a functioning diaphragm in patients with generalized muscle wasting and that change in thickness or thickness fraction might be more definitive. It would be reasonable to do future studies for further details. (Guttesman et al, 1997)

Most of the studies (e.g. DiNino, Ferrari), the authors affirm to prefer right hemidiaphragm because the better acoustic window provided by the liver makes easier to acquire the measure of tdi, however in the current study the analysis of the tdi in the apposition zone is technically possible both right and left, because the acoustic window is the same (between ultrasound probe and diaphragm there is only thoracic wall).

Limitations of the Study

Our study has some limitations. The first is that, we didn't perform comparison with other methods that may be considered as gold standard in the assessment of diaphragmatic function e.g. transdiaphragmatic pressure, phrenic nerve stimulation studies, electromyography. These methods are invasive; require special equipments and a well-trained and specialized team. Also it carries the risk of pneumothorax in compromised critically ill patients especially in case of hyperinflation as in COPD. Furthermore, other studies already concluded that diaphragm ultrasound is a reliable method to evaluate its respiratory function. (Nava et al, 1994 and Summerhil et al, 2008)

Secondly, Ultrasound measurements were performed only at the beginning of the SBT. It's possible that some patients with DTF <29% before extubation and were successfully weaned may have a DTF >29% after that if we considered a contribution from ventilator induced diaphragmatic dysfunction. Also it's possible that some patients with DTF >29% before extubation and failed weaning may have a DTF <29% after that as sometimes the inspiratory load that is tolerable at the beginning of the trial increase throughout the trial. Further studies needed to evaluate DTF at different times of the SBT.

5. Conclusions

Ultrasound measurement of diaphragmatic thickness fraction may predict weaning outcome in COPD similar to other established weaning parameters. It is a simple, rapid and non-invasive test that can be repeated several times without any risk for patients. It represents an easy-to-obtain new weaning index that can be introduced, if further validated by other studies, as a bedside method in the clinical practice.

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