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Article

Correlation between the P0.1 and diaphragmatic thickness fraction by ultrasound in assessment of patients' ventilatory drive

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Abstract. *Background:* The diaphragm is the main muscle that powers breathing. The relative contribution of the patient's effort during assisted breathing is difficult to measure in clinical conditions, and the diaphragm, the major muscle of inspiratory function, is inaccessible to direct clinical assessment. Several methods have been used in the research setting to assess diaphragmatic contractile activity. We studied the correlation between the p0.1 and diaphragmatic thickness fraction by ultrasound to assess the patient's relative contribution in breathing during mechanical.

Material and methods: In this observational study,50 mechanically ventilated patients were examined by the ultasound to measure the diaphragmatic thickness fraction which was statistically correlated with the p0.1 measured on the ventilator.

Results: There is no significant statistical correlation between average P0.1, DTF, RSBI in either total, supported ventilation group or mandatory ventilation group. The only found statistically significant correlation is a negative one between P0.1 and RSBI. The ROC curve for Combination of average P0.1 of more than or equal to 0, average DTF of 26 or more and RSBI of 40 or less can predict extubation in the total studied cases, the supported ventilation group and the mandatory ventilation group with a statistically significant P value in each category.

Conclusions: Diaphragm thickening fraction of the right diaphragm by ultrasound of more than or equal to 26% combined with RSBI of less than or equal to 40 together with P0.1 of 0 or more have improved the efficacy for prediction of successful weaning. Point-of-care ultrasound to assess diaphragm function has a steep learning curve but is ultimately achievable with excellent reproducibility. This combination between variables could help physicians decrease the ventilatory support in critically ill patients and is relatively easy to manage and cost effective.

Keywords: diaphragmatic thickness fraction, ultrasound, P0.1,RSBI, ventilatory drive, patient contribution in respiration.

Introduction

The diaphragm is the main muscle that powers breathing. Impaired function of the diaphragm can lead to respiratory complications and often prolongs the duration of mechanical ventilation(1). Conversely, mechanical ventilation itself may lead to diaphragm atrophy and dysfunction, which are well-recognized features of critically-ill patients (2, 3). Assisted mechanical ventilation, such as pressure-support ventilation (PSV), is widely used in critically ill patients with the aim of unloading the respiratory muscles while avoiding muscle atrophy (4). In such modes, a variable amount of work is generated by the patient's inspiratory muscles while the remainder is provided by the ventilator (5). Low levels of assistance may lead to fatigue and discomfort, while over-assistance can generate patient-ventilator asynchrony (6), and mechanical ventilator-induced diaphragm dysfunction (7).

The relative contribution of the patient's effort during assisted breathing is difficult to measure in clinical conditions, and the diaphragm, the major muscle of inspiratory function, is inaccessible to direct clinical assessment. Several methods have been used in the research setting to assess diaphragmatic contractile activity (8). Among these, the standard reference is represented by the measurement of pleural (or esophageal (P_{es}) and abdominal (or gastric (P_{ga}) pressures and variables derived from those measurements (9). However, such methods are still far from routine clinical practice, thus highlighting the need for simple and accurate methods to assess diaphragmatic performance in critically ill patients.

The airway occlusion pressure, P0.1, is an index for the neuro-muscular activation of the respiratory system. It has been shown to be a very useful indicator for the ability of patients receiving ventilatory support to be weaned from mechanical ventilation. Since the standard measurement technically complex, it is not widely available for clinical purposes.

The pressure generated during the first 0.1 second of an airway occlusion is widely used as an index of respiratory center motor output. During resting breath in normal subjects, P0.1 is approximately 0.5 to 1.5 cmH_2O.

For that reason a P0.1 measurement technique was developed as an integrated function in a standard respirator but unfortunately not in all respirators.Standard P0.1 measurement techniques are based on a total occlusion of the inspiration for more than 100 msec. These measurements are technically complex and therefore not useful for clinical purposes. Furthermore, a significant breath-by-breath variability has been shown for P0.1, which is neglected by any single point measurement technique. Some ventilators have developed a continuous on-line measurement for breath-by-breath determination of P0.1 as for example the Siemens Servo 900C respirator.

In triggered mechanical ventilation the delay time between the onset of the patient's inspiration and flow delivery from the respiratory is more than 100 msec for this respirator. During that time the inspiration is occluded. Therefore, the trigger effort was proposed to be a good estimate of P0.1. Based on this, P0.1 is calculated as follows: airway pressure (Paw) was registered at the patient's tubings site of the respiratory tubing, digitized and acquired by a personal computer at 100 Hz (10).

The recorder output of the ventilator was connected to the same computer, delivering the electronical signal for the inspiratory valve to open when the inspiratory effort has exceeded the trigger threshold, which needs a minimal delay time of 80 msec. Around 20 msec after this signal flow is delivered from the respirator (11).

From these data it is concluded that the described method for continuous P0.1 measurement provides reliable values with the advantage of a maneuver-free, breath-by-breath measurement technique. It thereby opens the possibility for monitoring the neuro-muscular activation of the respiratory system at the bedside, which is shown as an example for a patient during weaning from mechanical ventilation (12).

Bedside ultrasonography, which is already crucial in several aspects of critical illness(13), has been recently proposed as a simple, non-invasive method of quantification of diaphragmatic contractile activity (14). Ultrasound can be used to determine diaphragm excursion (15, 16), which may help to identify patients with diaphragm dysfunction (17). Ultrasonographic examination can also allow for the direct visualization of the diaphragm thickness in its zone of apposition (18). Thickening during active breathing has been proposed to reflect the magnitude of diaphragmatic effort, similarly to the ejection fraction of the heart(19).

The vast majority of reports addressing these ultrasonic indices were performed in spontaneously breathing patients (20, 21), and the behavior of these measurements in patients undergoing mechanical ventilation has not yet been fully evaluated. Some studies used diaphragmatic thickness fraction as a reliable weaning index (22).

Aim of the study

1. To assess the correlation between the diaphragmatic thickness fraction by ultrasonography, P0.1, and RSBI in the assessment of patients' contribution in mechanical ventilation.
2. To assess these markers alone or in combination in prediction of extubation in the total studied group and the 2 subgroups.

Materials and methods

Patients admitted to the Critical CareMedicine department requiring mechanical ventilation over 9 months. Exclusion criteria were history of diaphragmatic or neuromuscular disease, patients who had undergone recent thoracoabdominal surgeries,morbidly obese patients, hemodynamically unstable patients, high positive end expiratory pressure (PEEP) and intrinsic PEEP. After institutional ethics approval, an informed consent will be taken from the patient's family. The following data was collected: date of admission, age, sex, cause of ventilation.Vital signs during the study was also documented: Heart rate, Respiratory rate, Mean arterial blood pressure together with the ventilator data, Mode of mechanical ventilation, Tidal volume, Respiratory rate, Intrinsic PEEP, Inspiratory pressure.

This study was scheduled as follows,If the above baseline criteria are met, then explain the procedure to the patient and measure the diaphragmatic thickness fraction (DTF):Thickness at end inspiration-Thickness at end expiration/Thickness at end expiration.Technical Aspects of Measuring Diaphragmatic ThicknessReal time movement of the diaphragm will be recorded by B-mode ultrasonography using a 7-12 MHZ ultrasound linear transducer.(Mindray, digital ultrasonic diagnostic imaging system, model DP 20, SHENZHEN, MINDRAY BIO-MEDICAL CO, LTD,CHINA) Locate the Diaphragm at the Zone of Apposition to the Rib Cage. Patients will lie in the supine position.In cases where the head of the bed could not be laid completely flat due to the patient's condition, the degree of inclination (usually between 10 and 20 degrees) during baseline reading will be noted and the same degree of inclination will be set for all subsequent readingsThe probe will be oriented with the screen image by applying pressure to one end and noting the position of the image on the screen.The probe will be placed in the 8th or 9th right intercostal space in the midaxillary or anterior axillary line.The ultrasound beam will be directed perpendicular to the diaphragm; the probe will be positioned perpendicular to the chest wall in a longitudinal axis configuration with the left end cephalad, medially and dorsally directed.The probe will be adjusted until the diaphragm could be clearly visualized (small changes in orientation of probe from its ideal position results in distortion or loss of the image).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 (two dimensional) ultrasonography.End expiratory diaphragmatic thickness was measured in three consecutive respiratory cycles during the end of expiration, when the diaphragm is relaxed. End inspiratory diaphragmatic thickness was measured in three consecutive respiratory cycles during the end inspiratory pause.Thickness of the pleural and peritoneal membranes are exaggerated by ultrasound. Hence, to obtain the most accurate measurementof the diaphragmatic thickness, measurements was made from the middle of the pleural line to the middle of the peritoneal line.The DTF was calculated as a percentage from the following formula:Thickness at end inspiration-Thickness at end expiration/Thickness at end expiration.

The airway occlusion pressure, P0.1Subjects was placed in a supine position in a quiet room.Subjects were breathing calmly for 3 minutes. After 1 minute, the p0.1 values was measured every 30 seconds for the remaining 2 minutes following the initial measurement.All measurements was performed by a single operator experienced with the airway occlusion device. P0.1 was easily measured using the shutter in the ventilator's inspiratory line (already present in the ventilator), as near as possible to the patient, and recording airway pressure tracing at the Y piece.In patients ventilated using assist-control or pressure-support ventilation it was possible to use the demand valve system's prolonged time of response to obtain p0.1 breath-by-breath measurement.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

The used tests were Chi-square test:For categorical variables, to compare between different groups, Mann Whitney test:For abnormally distributed quantitative variables, to compare between two studied groups, Spearman coefficient:To correlate between two distributed abnormally quantitative variable, Receiver operating characteristic curve (ROC):It is generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests. SensitivityThe capacity of the test to correctly identify diseased individuals in a population "TRUE POSITIVES". The greater the sensitivity, the smaller the number of unidentified case "false negatives"- SpecificityThe capacity of the test to correctly exclude individuals who are free of the disease "TRUE NEGATIVES". The greater the specificity, the fewer "false positives" will be included - Positive Predictive value (PPV)The probability of the disease being present, among those with positive diagnostic test results– Negative Predictive value (NPV)The probability that the disease was absent, among those whose diagnostic test results were negative

Sample size was done in alexandria reasearch center.The minimum sample size required to achieve 80% study power and 95% confidence limits was 50 patients using Medcale 12.4.0 software.

The age of the studied population ranged between 11 and 90 with a mean of 48 years. 60 percent were males while the remaining 40 percent were females. 80 percent were mechanically ventilated using nemovent ventilator. Classification of the studied patients according to their etiology showed that the most two causes were DLC and RTA with 38% and 26% respectively. Most cases were examined within 10 days of admission(68%), about 18%were less than 4 days. These variables should be kept into consideration if we compare our results to others. 31 cases were ventilated by mandatory modes.This represents about 62% of cases. Only 19 cases received a supported ventilation by PSV which represents 38%.It is found that There is no significant statistical correlation between average P0.1, DTF, RSBI in either total, supported ventilation group or mandatory ventilation group.The only found statistically significant correlation is a negative one between P0.1 and RSBI with a P value <0.001. The ROC curve for Combination of average P0.1 of more than or equal to 0, average DTF of 26 or more and RSBI of 40 or less can predict extubation in the total studied patients holds a statistically significant P value of <0.001 with a confidence interval ranging between 0.746-0.958 with an AUC of 0.852 representing 76% sensitivity, 75.68% specificity, 52.6% PPV and 90% NPV. While that in the mandatory ventilation group holds a statistically significant P value of 0.021 with a confidence interval ranging between 0.649-0.965 representing 83% sensitivity, 64% specificity, 35.7% PPV and 94% NPV.Moreover, The ROC curve for Combination of average P0.1 of more than or equal to 0, average DTF of 26 or more and RSBI of 40 or less can predict extubation in the supported ventilation group holds a statistically significant P value of 0.014 with a confidence interval ranging between 0.665 – 1.000 with an AUC of 0.845 which holds 85% sensitivity, 75 % specificity, 66.7% PPV and 90% NPV.

Results

Comparison

Table (1): Distribution of the studied cases according to mode of MV in total sample (n = 50)

Mode of MV	No.	%
Supported ventilation group (PSV)	19	38.0
Mandatory ventilation group	31	62.0

The studied cases were distributed according to their mode of mechanical ventilation into 2 groups. The first is the supported ventilation group with 19 cases which represent 38% of the total studied cases. The second and last group is the mandatory ventilation group with 31 cases which represents 62% of the total studied cases.

Table (2): Distribution of the studied cases according to ICU in total sample (n = 50)

ICU	No.	%
INT medicine	4	8.0
ICU-1	10	20.0
ICU-2	5	10.0
ICU-3	18	36.0
ICU-4	6	12.0
ICU-5	7	14.0

ICU3 had most studied cases with about 36 cases (36%), while the least percentage of cases were in the internal medicine ICU with only 4 cases (8%).

Table (3): Distribution of the studied cases according to Type of ventilator in total sample (n = 50)

Type of ventilator	No.	%
Bellavista	6	12.0
Drager	2	4.0
GE engstrom pro	1	2.0
Hamilton G5	1	2.0
Nemovent	40	80.0

80% of the studied cases were ventilated by a **Nemovent** ventilator which represents 80% of cases.

Table (4): Comparison between the two studied groups according to outcome, average p0.1, average DTF and RSBI

	Total (n = 50)		**Mode of MV**				**Test of Sig.**	**p**
			Supported ventilation group (PSV) (n = 19)		**Mandatory ventilation group (n = 31)**			
	No.	**%**	**No.**	**%**	**No.**	**%**		
Outcome								
Un-extubated	37	74.0	12	63.2	25	80.6	χ^2= 1.872	^{FE}p= 0.199
Extubated	13	26.0	7	36.8	6	19.4		
Average $p_{0.1}$								
Min. – Max.	-4.0 – 2.77		-2.57 – 2.77		-4.0 – 2.07		U= 288.0	0.897
Mean ± SD.	-0.17 ± 1.24		-0.11 ± 1.25		-0.20 ± 1.26			
Median (IQR)	-0.12(-0.73 – 0.40)		-0.10 (-0.77 – 0.38)		-0.13 (-0.58 – 0.37)			
Average DTF								
Min. – Max.	13.54 – 90.35		14.52 – 90.35		13.54 – 62.73		U= 273.0	0.667
Mean ± SD.	36.28 ± 15.81		37.78 ± 21.39		35.36 ± 11.47			
Median (IQR)	33.23(26.34 –41.11)		29.63(25.32 –40.29)		33.33(27.53 –41.27)			
RSBI								
Min. – Max.	10.0 – 90.0		10.0 – 90.0		16.34 – 80.0		U= 286.50	0.873
Mean ± SD.	38.56 ± 18.78		39.32 ± 22.73		38.09 ± 16.28			
Median (IQR)	32.22(25.0 – 52.5)		33.93 (21.5 – 56.8)		32.0 (27.9 – 46.0)			

χ^2: **Chi square test** FE: **Fisher Exact**
U: Mann Whitney test IQR: **Inter quartile range**
p: p value for comparing between the studied groups

In the total number of patients, the average P0.1 ranged from -4 to 2.77 with a mean of -0.17, whereas the average DTF ranged from 13.5 to 90% with a range of 36%. As for RSBI, its values ranged from 10 to 90 with a mean of 38.5.

Table (5): Comparison between the two studied groups according to demographic data

	Total (n = 50)		Mode of MV					
			Supported ventilation group (PSV) (n = 19)		Mandatory ventilation group (n = 31)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Sex								
Male	30	60.0	12	63.2	18	58.1	χ^2= 0.127	0.721
Female	20	40.0	7	36.8	13	41.9		
Age								
Min. – Max.	11.0 – 90.0		19.0 – 80.0		11.0 – 90.0		U= 248.0	0.352
Mean ± SD.	48.46 ± 21.57		52.11 ± 20.61		46.23 ± 22.16			
Median (IQR)	50.0 (27.0 – 65.0)		50.0 (34.0 – 74.5)		40.0 (26.5 – 62.0)			

χ^2: **Chi square test**
U: Mann Whitney test
IQR: **Inter quartile range**
p: p value for comparing between the studied groups

Regarding the sex, 60% of the studied patients were males while the remaining 4% were females. As for the age, it ranged from 11 to 90 years with a mean of 48 years.

Table (6): Comparison between the two studied groups according to days of examination

Days of examination	Total (n = 50)		Mode of MV				Test of Sig.	p
			Supported ventilation group (PSV) (n = 19)		**Mandatory ventilation group (n = 31)**			
	No.	**%**	**No.**	**%**	**No.**	**%**		
≤10 days from admission	31	62.0	11	57.9	20	64.5	χ^2= 0.219	0.640
>10 days	19	38.0	8	42.1	11	35.5		
Min. – Max.	0.0 – 365.0		0.0 – 30.0		0.0 – 365.0		U= 253.50	0.410
Mean ± SD.	16.20 ± 51.18		10.53 ± 9.56		19.68 ± 64.73			
Median (IQR)	5.50 (1.0 – 18.0)		7.0 (2.0 – 18.50)		5.0 (1.0 – 13.0)			

χ^2: **Chi square test**
U: Mann Whitney test
IQR: **Inter quartile range**
p: p value for comparing between the studied groups

62% of cases were examined within 10 days of admission, while the rest were examined with in more than 10 days with a mean of 16 days.

Relation

Table (7): Correlation between average p0.1 with average DTF and RSBI in each group

	Total (n = 50)		Mode of MV			
			Supported ventilation group (PSV) (n = 19)		**Mandatory ventilation group (n = 31)**	
	r_s	**P**	**r_s**	**p**	**r_s**	**p**
Average $p_{0.1}$ vs. DTF	-0.093	0.521	-0.382	0.107	0.105	0.575
Average $p_{0.1}$ vs. RSBI	-0.231	0.107	0.216	0.375	-0.629	<0.001*
Average DTF vs. RSBI	-0.072	0.617	-0.140	0.567	-0.058	0.755

r_s: Spearman coefficient

*: Statistically significant at $p \le 0.05$

There is no significant statistical correlation between average P0.1, DTF, RSBI in either total, supported ventilation group or mandatory ventilation group.

The only found statistically significant correlation is a negative one between P0.1 and RSBI with a P value <0.001.

Table (8): Relation between outcome with average p0.1 and average DTF in each group

		Outcome		U	p
		Un-extubated	**Extubated**		
Total (n = 50)	**Average $p_{0.1}$**	**(n = 37)**	**(n = 13)**		
	Min. – Max.	-4.0 – 2.07	-0.80 – 2.77	222.50	0.690
	Mean ± SD.	-0.25 ± 1.33	0.07 ± 0.94		
	Median	-0.13	-0.10		
	Average DTF	**(n = 37)**	**(n = 13)**		
	Min. – Max.	13.54 – 62.73	14.52 – 90.35	199.50	0.364
	Mean ± SD.	33.82 ± 11.45	43.28 ± 23.57		
	Median	32.69	34.70		
Supported ventilation group (PSV) (n = 19)	**Average $p_{0.1}$**	**(n = 12)**	**(n = 7)**		
	Min. – Max.	-2.57 – 1.67	-0.80 – 2.77	20.0	0.068
	Mean ± SD.	-0.47 ± 1.22	0.51 ± 1.11		
	Median	-0.53	0.37		
	Average DTF	**(n = 12)**	**(n = 7)**		
	Min. – Max.	14.81 – 56.98	14.52 – 90.35	34.0	0.536
	Mean ± SD.	31.50 ± 10.92	48.56 ± 30.65		
	Median	28.99	34.70		
Mandatory ventilation group (n = 31)	**Average $p_{0.1}$**	**(n = 25)**	**(n = 6)**		
	Min. – Max.	-4.0 – 2.07	-0.73 – -0.10	46.0	0.158
	Mean ± SD.	-0.14 ± 1.40	-0.44 ± 0.26		
	Median	0.13	-0.55		
	Average DTF	**(n = 25)**	**(n = 6)**		
	Min. – Max.	13.54 – 62.73	23.22 – 55.77	65.50	0.643
	Mean ± SD.	34.94 ± 11.75	37.12 ± 11.05		
	Median	33.13	35.52		

U: Mann Whitney test

IQR: **Inter quartile range**

p: p value for comparing between **Un-extubated** and **extubated**

Table (9): Comparison between the two studied groups according to diagnosis

	Total (n = 50)		Mode of MV				χ^2	p
			Supported ventilation group (PSV) (n = 19)		**Mandatory ventilation group (n = 31)**			
	No.	**%**	**No.**	**%**	**No.**	**%**		
Diagnosis								
AKI	2	4.0	1	5.3	1	3.2	0.127	$^{FE}p=1.000$
TOXO	3	6.0	2	10.5	1	3.2	1.113	$^{FE}p=0.549$
RTA	13	26.0	5	26.3	8	25.8	0.002	$^{FE}p=1.000$
GB	1	2.0	0	0.0	1	3.2	0.625	$^{FE}p=1.000$
Intra-abdominal sepsis	1	2.0	1	5.3	0	0.0	1.665	$^{FE}p=0.380$
DLC-CVS	19	38.0	8	42.1	11	35.5	0.219	0.640
DLC-CP	1	2.0	0	0.0	1	3.2	0.625	$^{FE}p=1.000$
DLC viral encephalitis	1	2.0	0	0.0	1	3.2	0.625	$^{FE}p=1.000$
DLC Hypernatremia	1	2.0	0	0.0	1	3.2	0.625	$^{FE}p=1.000$
DLC for DD	1	2.0	0	0.0	1	3.2	0.625	$^{FE}p=1.000$
COPD exacerbation	2	4.0	1	5.3	1	3.2	0.127	$^{FE}p=1.000$
Cardiogenic shock	5	10.0	1	5.3	4	12.9	0.764	$^{FE}p=0.637$

χ^2: **Chi square test**

FE**: Fisher Exact**

p: p value for comparing between the studied groups

From this table, it is obvious that most frequent cases were DLC-CVS with 38% of total cases, followed by RTA with 26% of total cases and DLC.

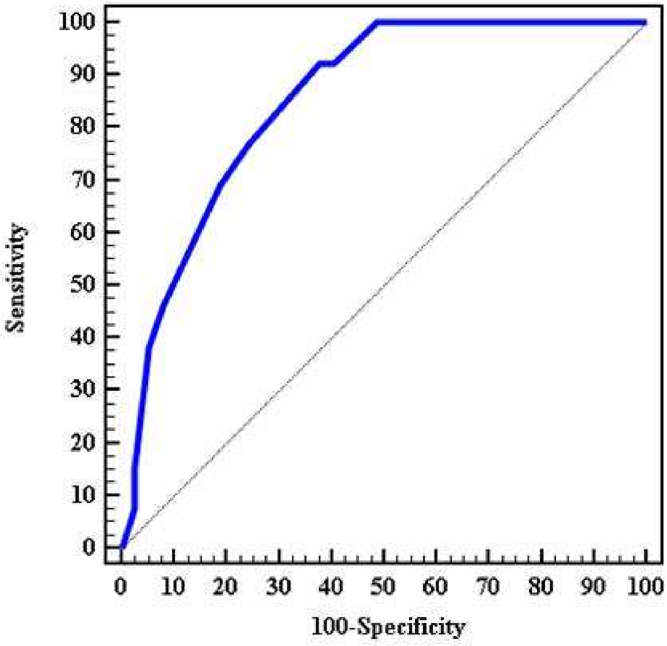

Figure (1): ROC curve for combination of average $p_{0.1}$, average DTF and RSBI to predict Extubated patients (n= 13) from Un-extubated (n = 37) in total sample

Table (10): Agreement (sensitivity, specificity) for combination of average p0.1, average DTF and RSBI to predict Extubated patients (n = 13) from Un-extubated (n = 37) in total sample

Combination of	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Average DTF, $p_{0.1}$ and RSBI	0.852	<0.001*	0.746 – 0.958	DTF ≥26 $P_{0.1}$ ≥0 RSBI ≤40	76.92	75.68	52.6	90.3

AUC: Area Under a Curve

p value: Probability value

CI: Confidence Intervals

NPV: Negative predictive value

PPV: Positive predictive value

The ROC curve for Combination of average P0.1 of more than or equal to 0, average DTF of 26 or more and RSBI of 40 or less can predict extubation in the total studied patients holds a statistically significant P value of <0.001 with a confidence interval ranging between 0.746-0.958 with an AUC of 0.852 which holds 76% sensitivity, 75.68% specificity, 52.6% PPV and 90% NPV.

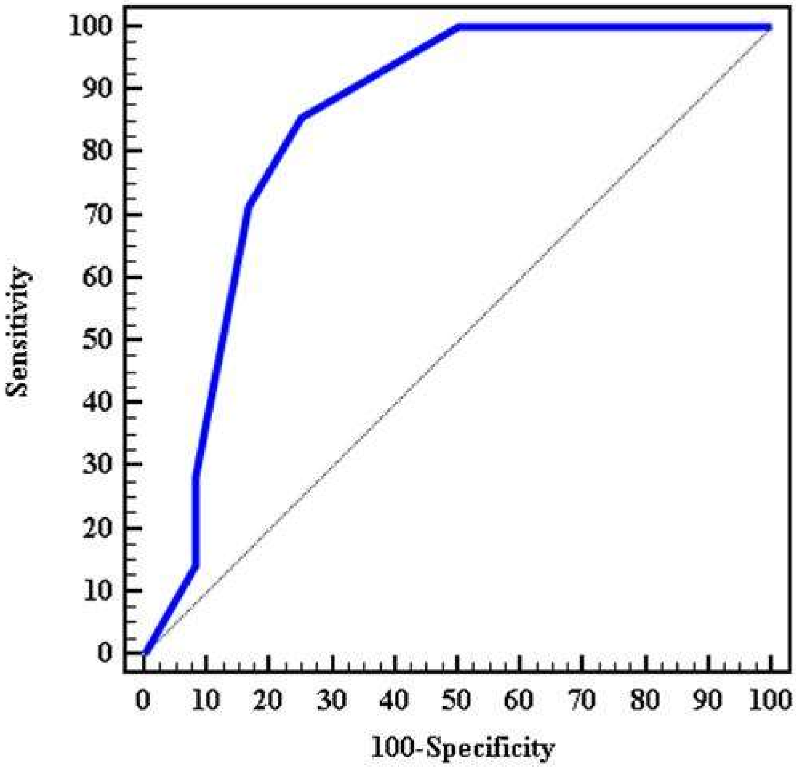

Figure (2): ROC curve for combination of average $p_{0.1}$, average DTF and RSBI to predict Extubated patients (n = 7) from Un-extubated (n = 12) in supported ventilation group (PSV) group

Table (11): Agreement (sensitivity, specificity) for combination of average p0.1, average DTF and RSBI to predict Extubated patients (n = 7) from Un-extubated (n = 12) in supported ventilation group (PSV) group

Combination of	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Average DTF, $p_{0.1}$ and RSBI	0.845	0.014*	0.665 – 1.000	DTF ≥26 $P_{0.1}$ ≥0 RSBI ≤40	85.71	75.00	66.7	90.0

AUC: Area Under a Curve p value: Probability value

CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

The ROC curve for Combination of average P0.1 of more than or equal to 0, average DTF of 26 or more and RSBI of 40 or less can predict extubation in the supported ventilation group holds a statistically significant P value of 0.014 with a confidence interval ranging between 0.665 – 1.000 with an AUC of 0.845 which holds 85% sensitivity, 75 % specificity, 66.7% PPV and 90% NPV.

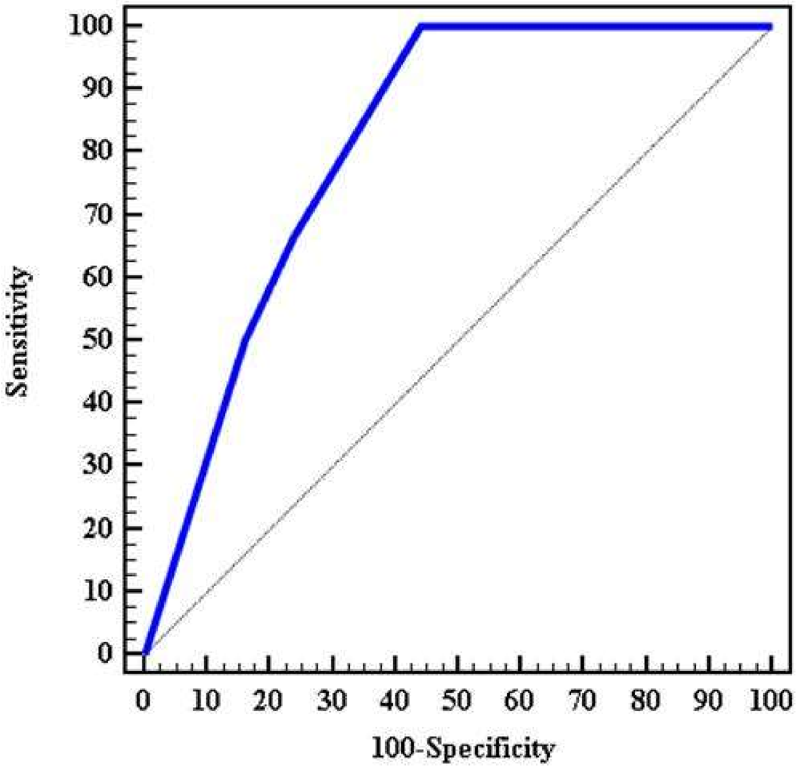

Figure (3): ROC curve for average $p_{0.1}$, average DTF and RSBI to predict Extubated patients (n = 6) from Un-extubated (n = 25) in mandatory ventilation group

Table (12): Agreement (sensitivity, specificity) for average p0.1, average DTF and RSBI to predict Extubated patients (n = 6) from Un-extubated (n = 25) in mandatory ventilation group

Combination of	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
Average DTF, $p_{0.1}$ and RSBI	0.813	0.019*	0.659 – 0.968	DTF ≥26 $P_{0.1}$ ≥0 RSBI ≤40	66.67	76.00	40.0	90.5

AUC: Area Under a Curve p value: Probability value
CI: Confidence Intervals
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$

The ROC curve for Combination of average P0.1 of more than or equal to 0, average DTF of 26 or more and RSBI of 40 or less can predict extubation in the mandatory ventilation group holds a statistically significant P value of 0.019 with a confidence interval ranging between 0.659 – 0.968 with an AUC of 0.813 which holds 66% sensitivity, 76 % specificity, 40% PPV and 90.5% NPV.

Discussion

The relative contribution of the patient's effort during assisted breathing is difficult to measure in clinical conditions, and the diaphragm, the major muscle of inspiratory function, is inaccessible to direct clinical assessment. Many non-invasive indices have been suggested to adjust the level of ventilatory support according to the patients' ventilatory drive, such as clinical assessment of accessory muscle activity (23), RR and Vt (24), the assessment of respiratory drive (P0.1) (25), or the pressure developed by the inspiratory muscles (PMI) (26). However, these indices either lack adequate sensitivity/specificity, or require a cooperative patient. Several methods have been used in the research setting to assess diaphragmatic contractile activity (27).

Among these, the standard reference is represented by the measurement of pleural (or esophageal (Pes)) and abdominal (or gastric (Pga)) pressures and 54variables derived from those measurements (9). Other conventional methods used to assess diaphragmatic function are the measurement of trans-diaphragmatic pressure (Pdi) and phrenic nerve stimulation. Also, fluoroscopy and electromyography have been largely used. However, all these methods are invasive and uncomfortable or expose the patients to radiations (22). However, such methods are still far from routine clinical practice, thus highlighting the need for accurate and simple methods to assess the performance of the diaphragm in critically ill patients. The evaluation of the diaphragmstic contractile activity by US is our main goal. Diaphragmatic ultrasound is a simple, rapid, reproducible, and non-invasive test that can be repeated several times without any risk for patients and provides important information on their respiratory function.

Matamis et al mentioned in their studies that ultrasound can be a modality which demonstrates the patient's initiation and completion of inspiratory effort in real time, obliterating the need for invasively inserting esophageal balloon catheters for that purpose in healthy volunteers and also in patients under assisted modes of ventilation confirm that diaphragmatic M-mode sonography provides a mirror image of the changes in esophageal pressur (14).

B-mode ultrasound may be used to assess the thickness of the muscle, as was demonstrated by Cohn and co-workers (28). Diaphragm thickness may also be estimated in M-mode, although this method was criticized (29). Nevertheless, Vivier and co-workers concluded that diaphragm thickness evaluated in M-mode is a non-invasive and reproducible ultrasound method, useful to evaluate muscle function and its contribution to respiratory workload (30). However, the great majority of diaphragm ultrasound studies have measured diaphragm thickness in B-mode (31).

In this study, we studied the diaphragm using B mode ultrasound. We found no statistically significant correlation between DTF, P0.1 and RSBI in all studied patients and the two subgroups of patients (supported ventilation group and the mandatory ventilation group) with the exception of the negative correlation between RSBI and P0.1 in the mandatory ventilation group.

Umbrello et al have also previously found no correlation between indices of diaphragm thickening and muscle effort, nor was the later correlated to diaphragm excursion (32). Moreover, they found a significant positive correlation between thickening fraction and both PTPes and PTPdi. Although most studies about assessment of diaphragm thickening by US are performed on spontaneously breathing patients (16, 20, 21, 33), Vivier et al demonstrated that diaphragmatic US might be useful for the assessment of the effort of breathing during non-invasive PSV (30).

Our results also show that after categorizing the studied sample size into two groups according to the mode of ventilation. There is no statistically significant difference between the supported ventilation group and the mandatory ventilation group as regards the outcome, average p0.1and average DTF.

In our study, 37 patients experienced failed extubation and were re-intubation and re-ventilated mechanically representing 74% of the study population. This is almost consistent to Ferrari et al. who reported 63% failure rate.(22) On the other side, Esteban et al. Baess et al. and Saeed et al. showed failure rate about 20%, 23.3% and 26.7 % respectively (34-36). This is explained because of the non uniform rule in study population selection with different causes of ventilation as well as different ventilation periods before extubation which may affect the outcome.

In this study, we did not find a single parameter cutoff point but we used a combination of parameters. The best cut off value for the combined parameters to predict extubation in the total studied patients are DTF of more than or equal 26, P0.1 of more than or equal 0 and RSBI of 40 or less these had a statistically significant P value of <0.001 with a confidence interval ranging between 0.746-0.958 with an AUC 0.852 which showed 76%sensitivity, 75%specificity, 52% PPV, 90% NPV.

In the supported ventilation group, the same combined cutoff points hold a statistically significant P value of 0.014 with a confidence interval ranging between 0.665 – 1.000 with an AUC of 0.845 which holds 85% sensitivity, 75 % specificity, 66.7% PPV and 90% NPV. While in the mandatory ventilated group the P value is 0.019 with a confidence interval ranging between 0.659 – 0.968 with an AUC of 0.813 which holds 66% sensitivity, 76 % specificity, 40% PPV and 90.5% NPV.

This is very close to the results found by Pirompanic et al in their study. They found the best cutoff value for predicting weaning successfulness was right DTF of more than or equal to 26%, which had the highest accuracy of 88.2%, specificity of 67.7%,sensitivity of 96.0% , NPV of 85.7% and PPV of 88.9%.Moreover,they used a combination cutoff points to validate their results and increase its specificity where they found The combination of right DTF of more than or equal to 26% together with RSBI less than or equal to 105 had an accuracy of 88.2%, specificity of 77.8%, sensitivity of 92.0%, NPV of 77.8% and PPV of 92.0%. (37). However, the accuracy of Pirompanic et al combination was not different from using DTF alone; this finding duplicates a previous study (38).

Furthermore, the cut off value of DTF by Osman et al was 28% showed 88.9% sensitivity, 100% specificity in our study (39). This is close to Baess et al. and DiNino et al. who reported 30 % DTF cut off value yet with sensitivity about 69.57%, 88% and specificity about 71.43%, 71% respectively (19, 35). This is in controversy to Ferrari. and Giovanni who reported a higher cut off value associated with succesful extubation and weaning equal to 36% and >36% respectively (22). On the contrary the study done by Umbrello et al. found lesser cut off value of 20% (32).

Although there are small changes regarding the diagnostic validity results comparing with the previously done trials, yet they all approve DTF as a good indicator for ventilatory drive and patients' contribution in ventilation.

Some authors as Osman et al, Umbrello et al. and Baess et al. compared DTF to diaphragmatic excursion. They found that the DTF was more reliable than excursion with higher sensitivity and higher efficacy and better AUC score (32, 35, 40).

Others as Soummer et al and Caltabeloti et al combined diaphragmatic ultrasound with lung ultrasound to increase their vallidity and specificity (41, 42).

Another study measured diaphragm thickness in patients with diaphragm paralysis to monitor recovery of the muscle over time. Interestingly, in this latter study, no increase in thickness was observed by ultrasound in patients who did not recover from paralysis, thus providing useful information for both diagnosing diaphragm paralysis and indicating recovery(43).

In the present study, the RSBI was ranging between 10 and 90 breath/min/L in the total sample. In the supported ventilation group, it ranged (10-90) while in the mandatory ventilated group, it ranged between 16.34 and 80 breath/min/L. Osman et al studied a different ppopulation where their RSBI ranged between 50 and 97 breath/min/L between in one group with 71.6 average value while the other group ranged between 105 and 125 breath/min/L with 113.9 average value (39). Saeed et al. found that patients with success weaning had average RSBI = 91 while those who failed weaning = 123.6.(36) The lesser accuracy of RSBI in predicting weaning successfulness could possibly be due to population diversity and perhaps a different ethnic group. Also it should be kept in mind that respiratory function declines gradually over a lifetime (44, 45), so the accuracy of RSBI might concurrently decrease with increased patient age.

As ultrasound is an operator-dependent method, some important techniques were used to decrease inter-observer variation. First, the patients' posture was similar in this study as much as possible and anatomical landmarks were applied for positioning the probe.

This combination could help physicians assess weaning readiness in critically ill patients, relatively easy to manage and cost effective.

Limitation

First the relatively small number of patients which have undergone the study. However, our results were in accordance with the previously mentioned studies even in a resource-limited setting as ours.

Being operator dependant is considered a limitation, however this is overcomed by its excellent learning curve in ultrasound in general and DTF measurement specifically, which was also mentioned by Pattarin Pirompanich and Sasithon Romsaiyut in their study(37).

Also, DTF measurement is difficult to be reproducible may be because a stable image is not easy to obtain especially if the patient is tachpnic as mentioned by Umbrello et al in their study (32).

Moreover, there are some limitations such as presence of pneumothorax as well as the morbid obesity which may interfere with best window for diaphragm visualization.

Another limitation is due to the exclusion criteria as patients with intrinsic PEEP or COPD. Also, we only assessed the right hemi-diaphragm because its visualization is easier as compared to the left side where imaging is sometimes impeded by gases in the GIT. Again, this limitation is common to other studies on ultrasonographic assessment of diaphragmatic contractile activity (30, 32). Another limitation is the poor acoustic window; which is reported to occur in a small percentage of cases, ranging between 2 and 10% (17, 30). Finally, we only included patients with PEEP <10 cmH2O. To date, there is no evidence about feasibility and accuracy of diaphragmatic ultrasonography in the presence of elevated levels of PEEP, where there might be a displacement of the superior edge of the zone of apposition (46).

Being an updated software, which is not present in all ventilaltors, the P0.1 is considered a limitation in the study together with its high variabilty and wide range which affects its validity.

Another limitation is that we did not compare with other methods that may be considered a gold standard in the assessment of diaphragmatic function, to validateour work, but this limitation can be overcomed by the previous study which found a good correlation between trans-diaphragmatic pressure-time product and DTF (30). Moreover, although trans-diaphragmatic pressure-time may be considered a gold standard in studies that evaluate new tests of diaphragmatic function, it is highly invasive and uncomfortable for the patient. Also, other studies already concluded that diaphragm ultrasound is a reliable method to evaluate its respiratory function, because measurements correlated well with lung volumes and with PImax (22).

In addition to that our study lacks the validity, reprodoucibility and generalization of the combined DTF,P0.1 and RSBI cutoff that we obtained. We have studied a very selected population from our ICU units.

Conclusions

Diaphragm thickening fraction of the right diaphragm by ultrasound of more than or equal to 26% combined with RSBI of less than or equal to 40 together with P0.1 of 0 or more have improved the efficacy for prediction of successful weaning. Point-of-care ultrasound to assess diaphragm function has a steep learning curve but is ultimately achievable with excellent reproducibility. This combination between variables could help physicians decrease the ventilatory support in critically ill patients and is relatively easy to manage and cost effective.

Recommendations

- Generalization of thhe study on a wider scale of different population to validate the correlation between DTF,RSBI and P0.1 and validate the cut off point between these indices.
- Comparison to a gold standard like Tdi to validate the DTF cut off points alone or in combination to P0.1 and RSBI
- Expansion of the studies performed on the effect of PEEP on diaphragmatic mobility and contractile action.
- Validation of the P0.1 readings on the different ventilator types.

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