Journal of Anesthesia and Clinical Research

Nassar et al., J Anesth Clin Res 2018, 9:5
DOI: 10.4172/2155-6148.1000824

Research Article Open Access

Evaluation of Ventilator-induced Diaphragmatic Dysfunction by Diaphragmatic Excursion During Spontaneous Breathing Trials

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Received date: April 16, 2018; **Accepted date:** May 14, 2018; **Published date:** May 18, 2018

Abstract

Introduction: Ventilator-induced diaphragmatic dysfunction (VIDD) leads to difficulties in weaning. Diaphragmatic excursion assessment by ultrasonography is a feasible bedside assessment of the diaphragm in the ICU. Our primary aim was to identify the presence of VIDD using US in patients undergoing Spontaneous breathing trials (SBT). Our secondary aim was to assess the impact of VIDD impact on weaning outcome.

Methods: This study was conducted in the Critical Care Department of Cairo University Hospital between March 2014 and March 2015. All consecutive subjects who required MV for ≥ 72 h and were ready for SBT were prospectively recruited. Exclusion criteria: Any history of aminoglycoside use, paralytics, central or neuromuscular disease, chemotherapy, cachexia, severe electrolyte imbalance or intra-abdominal pressure (IAP)>10 mmHg Thirty minutes from the start of SBT, each hemi-diaphragm was evaluated by M-mode sonography with the patient in the supine position. Five measurements were recorded and averaged. Ventilator Induced diaphragmatic dysfunction (VIDD) was diagnosed if diaphragmatic excursion (DE) was <10 mm. Patients were classified into two groups: the non-diaphragmatic dysfunction (NDD) group and the VIDD group. Patients were monitored for weaning and 30 day mortality.

Results: Fifty subjects (100%) were studied. The VIDD group included 24 (48%) subjects, and the NDD group included 26 (52%) subjects. There were no significant differences in age, sex, weight or comorbidities between the two groups (p>0.05). Successful weaning was present in [18/26 (69%) *vs.* 13/24 (54.2%), p=0.06] and weaning time was shorter [29 ± 18 *vs.* 43 ± 28 h, p=0.02] in the NDD group versus the VIDD group respectively. The median DE was higher in successfully weaned *vs.* failed weaning subjects [14.4 (1.9-40) *vs.* 9.2 (6.6-35.1), p=0.01]. The receiver operator characteristic curves (ROC) showed a cut-off for weaning DE 14 mm for right hemi-diaphragm with an area under the curve (AUC) 0.8.

Conclusions: VIDD is present in nearly half of our mechanically ventilated patients ≥ 72 h. VIDD is associated with lower DE and longer weaning time. Diaphragmatic excursion may serve as a valuable tool for predicting weaning outcome as traditional volumetric respiratory indices.

Keywords: Ventilator induced diaphragm dysfunction; Diaphragmatic excursion; Ultrasound diaphragm

Abbreviations: ABG: Arterial Blood Gases; BP: Blood Pressure; CBC: Complete Blood Count; CMV: Continuous Mandatory Ventilation; COPD: Chronic Obstructive Pulmonary Disease; CROP: Compliance Respiratory Rate, Oxygenation Pressure Index; DD: Diaphragmatic Dysfunction; DE: Diaphragmatic Excursion; DIA: Diaphragmatic Inspiratory Amplitude; HR: Heart Rate; IAP: Intra-Abdominal Pressure; IQR: Inter Quartile Range; MIP: Maximum Inspiratory Pressure; MV: Mechanical Ventilation; NDD: Non Diaphragmatic Dysfunction; P0.1: Airway Occlusion Pressure; PS: Pressure Support; ROC: Receiver Operator Characteristics; RR: Respiratory Rate; RSBI: Rapid Shallow Breathing Index; SBT: Spontaneous Breathing Trial; Spont Min Vent: Spontaneous Minute Ventilation; TLC: Total Leucocytic Count; US: Ultra Sound; VIDD: Ventilator Induced Diaphragmatic Dysfunction

Introduction

Difficulties in discontinuing ventilatory support are encountered in 20% to 25% of all mechanically ventilated patients [1] and approximately 40% of the total ventilation time is spent in weaning [2]. Diaphragmatic dysfunction (DD) plays a fundamental role in ventilator dependency [3-8]. Patients with adequate spontaneous tidal volume but poor diaphragmatic excursion (DE) are more likely to fail a breathing trial than are patients with adequate spontaneous tidal volume and good diaphragmatic movement [3]. Mechanical ventilation can induce DD by decreasing the force-generating capacity of the diaphragm [4]. This phenomenon is commonly termed ventilator-induced diaphragmatic dysfunction (VIDD) [5].

Mechanical ventilation in the controlled mode and possibly with high levels of partial ventilatory assist can result in VIDD [6]. Levin's landmark study demonstrated that 18 to 69 h of continuous mandatory ventilation (CMV) resulted in decreases in diaphragm fibre cross-sectional areas of 57% and 53% in type I and type II fibres, respectively [7]. The complete diaphragm muscle inactivity during CMV induces a

rapid decline in diaphragm muscle function associated with marked atrophy of both slow-and fast-twitch fibres in the diaphragms of an MV group compared to controls, whereas no such differences were observed in the pectoral muscles [7]. MV itself likely activates diaphragm autophagy via oxidative stress, thus contributing to the development of diaphragm muscle fibre atrophy and dysfunction [8].

Ultrasound (US) is a promising technique for evaluating the structure and dynamic function of the diaphragm. It is accurate, reproducible, easy to learn, portable, suitable for critically ill patients on mechanical ventilation, and uses no ionizing radiation [9].

Aim of the Work

Our primary aim was to identify the presence of VIDD using US in subjects undergoing Spontaneous breathing trials (SBT) after mechanical ventilation ≥ 72 h. Our secondary aim was to assess the impact of VIDD impact on weaning outcome.

Subjects and Methods

This prospective observational study was conducted in the Critical Care Department of Cairo University. Fifty subjects were consecutively recruited between March 1, 2014 and March 1, 2015.

Inclusion criteria: All subjects who underwent MV for ≥ 72 h and became eligible to undergo a spontaneous breathing trial (SBT) were immediately recruited to enter the study. Subjects were considered eligible for an SBT when they met all the following criteria: PaO_2/FiO_2>200, respiratory rate <30 breaths per minute, absence of fever, alert and cooperative, and haemodynamic stability without any vasoconstrictors [10].

Volume control ventilation was initially used as the mode of ventilation before the SBT. The SBT was performed by placing the patient on PS 10, PEEP 5 and FiO_2 0.5 for a period of 1 h.

The patients' next of kin or legal guardians signed informed consent documents to participate in this study involving human participants and for permitting the publication and reporting of participating patient data in any form.

Exclusion criteria: We excluded subjects who had any history of phrenic nerve palsy, diaphragmatic surgery, injuries involving the brainstem or cervical spine, neuromuscular disease (myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis), rhabdomyolysis, electrolyte imbalances, intra-abdominal pressure (IAP) >7 or who had been administered aminoglycosides, muscle-paralyzing agents or any sedative other than morphine during their hospital stay.

Methods

Parameters recorded at the beginning of and after 30 min of SBT:

Respiratory rate (RR), Tidal volume (VT), Spontaneous minute ventilation (Spont Min Vent) and arterial blood gases (ABG) including: pH, HCO_3, PaO_2, SaO_2 and FiO_2.

Rapid shallow breathing index (RSBI=f/VT); a respiratory rate ratio of <105 breaths/min/l has been considered as a good discriminator of weaning success and failure [11-14].

Compliance respiratory rate, oxygenation, pressure index (CROP index) The CROP index (ml × mmHg/breath per min/Kg) was calculated as [Cdyn × MIP × (PaO_2/PAO_2)]/RR, where Cdyn is dynamic compliance, PaO_2 is the partial pressure of arterial oxygen, PAO_2 is the partial pressure of alveolar oxygen, MIP is the maximal negative inspiratory pressure, and RR is the respiratory rate. A CROP index of ≥ 0.15 ml × mmHg/breath per min /Kg was considered a good predictor of successful extubation [15].

Airway occlusion pressure (P0.1) is determined by making an inspiratory effort against an occluded airway and then measuring the airway pressure 0.1 s after the initiation of the inspiratory effort. P0.1 is a measure of the intensity of the respiratory drive (normal P0.1 values are <2 cm H_2O). High values (>4-6 cm H_2O) indicate an abnormally high respiratory drive and therefore predict weaning failure [16].

Occlusion pressure and its ratio to maximum inspiratory pressure (P0.1/MIP ratio) relate the inspiratory drive and the effectiveness of muscular contraction during each breath to the maximum capacity to generate pressure. A value of <0.14 predicts successful weaning and extubation [17,18].

Measurement of DE by M-mode ultrasonography

Thirty minutes after the start of a 1 h SBT, five measurements were recorded and averaged. Measurements were performed in the supine position during a tidal inspiration of 6-12 ml/kg, excluding smaller or deeper breaths. The entire US examination was accomplished in 5 min [12]. The US examination was discontinued if the patient showed signs of respiratory fatigue. The evaluation was performed by a single well-trained expert physician who was not involved in patient management.

A 3.5-MHz US probe was placed over one of the lower intercostal spaces in the right anterior axillary line for the right hemi-diaphragm using a SonoScape US machine (S2BW, SonoScape Medical Corp. Shenzhen, China). The liver was used as a window for the right hemi-diaphragm. With the probe fixed on the chest wall during respiration, the US beam was directed to the hemi-diaphragmatic domes [11].

During inspiration, the normal diaphragm contracts and moves caudally towards the transducer; this is recorded as an upward motion in the M-mode tracing. The amplitude of excursion, termed the diaphragmatic inspiratory amplitude (DIA), was measured on the vertical axis of the tracing from the baseline to the point of maximal inspiration height on the graph.

Outcome assessment was performed for the following

VIDD was diagnosed if DE was ≤ 10 mm [13].

Patient Groups: subjects were classified into two groups, namely the NDD group (subjects with DE >10 mm) and the VIDD group (subjects with a DE ≤ 10 mm).

Weaning Success was defined as a state in which a patient was able to maintain his or her own breathing for 48 hrs without any ventilator support.

Weaning failure was defined as a requirement for MV within 48 h of unassisted breathing, or failure of SBT. Failure of SBT was defined as a change in mental status, onset of discomfort, diaphoresis, RR >35 breaths/min, haemodynamic instability (heart rate >140, systolic blood pressure >180 or <90 mmHg), or signs of increased labour in breathing 18.

Total ventilation time was defined as the period between the start and end of MV.

Weaning time was defined as the time spent in a partial support mode, such as pressure support or continuous positive airway pressure. It was calculated as the total ventilation time minus the full support period, the latter representing the time spent either in volume-controlled or pressure-controlled mode [13].

ICU length of stay was monitored.

Thirty-day mortality was documented.

Statistical analysis

Data are presented as the mean ± SD or as the median and interquartile range (IQR) for continuous variables and as absolute or relative frequencies for categorical variables. Unpaired Student's t tests or Mann-Whitney U tests were used to compare continuous variables, and chi-square tests or Fisher's exact tests were used to compare categorical variables. Receiver operator characteristic curves (ROCs) were used to evaluate the diagnostic efficacy of ultrasonography DD for predicting weaning failure. A p value <0.05 was considered significant. All statistical analyses were performed using SPSS for Windows, version 19.0 (SPSS Inc., Chicago, IL).

Results

Demographic and clinical comorbidities

The study included a total of 50 subjects (mean age 51.6 ± 18.1; mean BMI 25 ± 5). The subjects included 27 males (54%), and diabetes was present in 35 (70%) of the subjects. The underlying cause of ICU admission was pneumonia in 19 patients (38%), chronic obstructive pulmonary disease flare (COPD) in 11 patients (22%), cerebrovascular stroke in 7 patients (14%), hypothyroid coma in 7 patients (14%), hepatocellular failure in 5 patients (10%), postoperative surgical complications in 5 patients (10%), septic shock in 4 patients (8%) and cardiogenic pulmonary oedema in 3 patients (6%) (Figure 1).

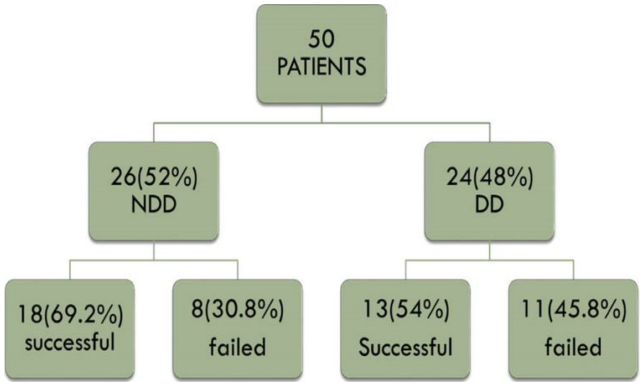

Figure 1: Flow diagram.

The NDD group included 26 (52%) subjects. The VIDD group included 24 (48%) subjects. There were no significant differences in age, sex, weight or comorbidities between the two groups (p>0.05) (Table 1). Rt. diaphragm mean excursion was greater 24.7 ± 8.7 mm *vs.* 7.6 ± 2.02 mm (p=0.01) in the NDD *vs.* VIDD groups, respectively.

Data	NDD n=26	DD n=24 (100%)	P value
Males	14	13	0.98
Females	12	11	0.9
Diabetes mellitus	17	16	0.9
Hypothyroidism	5	2	0.2
COPD	5	6	0.6
Stroke	1	6	0.06
Septic shock	3	1	0.71
Hepatic cell failure	2	3	0.31
Pulmonary edema	2	1	0.9
Chest infection	10	9	0.07
Post-operative monitoring	3	2	0.32
	Mean ± SD	Mean ± SD	
Age (yrs.)	50.6 ± 17.1	53.5 ± 17.4	0.6
BMI	25.2 ± 4.3	24.7 ± 4.9	0.47

Table 1: Demographic and Clinical Comorbidities.

$PaCO_2$ was higher (48.3 ± 8 *vs.* 37.6 ± 7, p=0.01) in the NDD group than in the VIDD group respectively. Other laboratory data PaO_2, pH, HCO_3 were not significantly different between the two groups (p>0.05).

Successful weaning was present in [18/26 (69%) *vs.* 13/24 (54.2%), p >0.05] while Weaning failure [8/26 (30.8%) *vs.* 11/24 (45.8%) p>0.05] in the NDD *vs.* VIDD groups, respectively. Spont Min Vent was higher in the NDD group than in the VIDD group (12.35 ± 4.22 L/min *vs.* 9.45 ± 2.28 L/min, respectively; p=0.017). Weaning time was shorter [29 ± 18 versus 43 ± 28 h, p=0.02] in the NDD group than in the DD group respectively. Successful weaning was associated with a higher median DE in successfully weaned *vs.* failed weaning subjects [14.4 (1.9-40) *vs.* 9.2 (6.6-35.1), respectively; p=0.01].

P0.1 (1.3 ± 0.8 mmHg *vs.* 1.7 ± 0.88 mmHg, respectively; p>0.05), P0.1/MIP ratio (0.24 ± 0.9 *vs.* 0.04 ± 0.03, p>0.05), CROP index (15 ± 9 *vs.* 18 ± 13 ml/breath/min, p>0.05), Total ventilation time (139 ± 38 versus 144 ± 48 h, p>0.05). ICU length of stay (7.2 ± 3.7 *vs.* 9.2 ± 4.8, p>0.05) and Thirty-day mortality [6/26 (20.3%) *vs.* 5/24 (23.1%), p>0.05] did not show any significant difference between the NDD versus VIDD groups respectively.

DE in relation to weaning outcome: The receiver operator characteristics (ROC) curve showed an optimal cut-off value of DE for predicting weaning success 14 mm for the right hemi-diaphragm with an area under curve (AUC) of 0.84 (Figure 2).

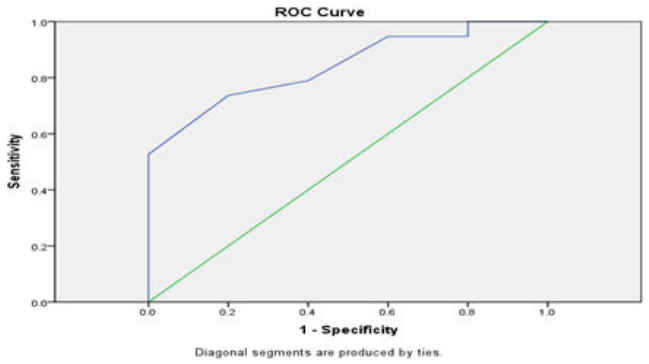

Figure 2: ROC of Rt. DE <14 mm, with an AUC of 0.84.

Discussion

During the evaluation of patients on partial ventilatory support, diaphragmatic M-mode ultrasonography can provide valuable information that can be helpful in monitoring clinical progress and predicting weaning. We identified the presence of VIDD using US in subjects undergoing Spontaneous breathing trials (SBT) after mechanical ventilation ≥ 72 h, and we assessed the impact of VIDD impact on weaning outcome.

A DE of <10 mm has been proposed as a diagnostic criterion for DD [13,19-26]. The optimal cut-off point for DD has been controversial. We used a cutoff reference of DE ≤ 10 mm, similar to that suggested in Kim's pioneering study on 82 medical ICU patients, although this value differs from that proposed by Lerolle et al. [27] (<25 mm). Lerolle et al. may have obtained a higher cutoff due to the cohort of prolonged (>7 days) mechanically ventilated post-cardiac surgery patients. Cardiac surgery is known to cause phrenic nerve injury during harvest of the left side internal mammary artery [28]. Which leads to diaphragmatic paralysis in 2-20% of patients [29]. In addition to the small sample size used in that study (28 patients), Lerolle et al. [27] measured DE during maximal voluntary inspiratory effort in a semi-sitting position, whereas we measured DE during tidal breathing in the supine position, which is preferred due to its lower overall variability, lower side-to-side variability, and greater reproducibility [13,22,27,30]. Older studies by Fedullo et al. [19] and DeVita et al. [31] reported DD (DE <16 mm) in post-cardiac surgery patients [19,31]. Various investigators measured mean DE over a wide range from 15 ± 2 to 18 ± 4 mm by longitudinal scanning [11,20,23-25] or from 14.4 to 21 ± 6 mm by transverse scanning [21,26]. In addition, they measured DE over 18 ± 4 mm while the patient was in a standing position [20]. These approaches lead to variations in transducer position on the chest or abdominal wall, thus affecting reproducibility, and they may be unable to record maximal DE due to the oblique direction of the US beam.

We recorded a high incidence of VIDD, with 24 patients (48%) falling into this group; this incidence is much higher than that obtained by Kim et al. which was 29%. Our study showed a nonsignificant weaning failure in the NDD group than in the DD group. Kim et al. [13] reported a higher overall weaning failure rate of 54/82 (66%) but, nonetheless, a lower rate in the NDD group than in the DD group [34/58 (59%) *vs.* 20/24 (83%), respectively; p<0.01] [13]. The differences in the incidence of DD and weaning outcome compared to those found in our study may be due to our having started measurements after ≥ 72 h of MV, whereas Kim et al. started measurements after only 48 h of MV [13].

The present study revealed that $PaCO_2$ was higher in the NDD group than in the DD group. Schellekens et al. [32] concluded that MV under hypercapnic conditions protects the diaphragm of rats from ventilator-induced diaphragm atrophy [32]. Other animal studies by Jung et al. [33] and Akca et al. [34] showed that hypercapnic acidosis largely diminished ventilator-induced inflammation in the diaphragm [33-38]. On the contrary, Jonville et al. [39] showed that $PaCO_2$ was significantly higher among patients with reduced diaphragmatic muscle contractility and a decreased intracellular pH. Jaber et al. [40] showed that even a short and acute exposure to hypercapnia acidosis can alter the contractile property of the diaphragm of piglets and lead to an increase in the respiratory muscle work. Our spontaneously breathing patients showed a relatively low level of hypercapnia (PCO_2 37 to 48 mmHg) in comparison to Jung et al. [33] ($PaCO_2$ 55 to 70 mmHg), Akca et al. [34] ($PaCO_2$ up to 60 mmHg), Jonville et al. [39] ($PaCO_2$ 51 mmHg) in healthy volunteers and Jaber [40] much higher levels ($PaCO_2$ up to 110 mmHg) showing that DD was proportionate to level of hypercapnia, and partially reversed 60 min after exposure [40]. These contradictory findings may be because of the different levels of hypercapnia assessed in those different studies, the different patient cohorts of diseased subjects or healthy volunteers, and also the difference from being on a controlled mode of ventilation or spontaneously breathing with active diaphragmatic function.

We reported a 30-day mortality of 22%, with no significant difference between the NDD and DD groups [6/26 (20.3%) *vs.* 5/24 (23.1%), respectively; p>0.05]. Kim et al. [13] reported a similar 30-day mortality of 19.5% in the NDD and DD groups [4/24 (16.66%) *vs.* 12/58 (20.6%), respectively; p>0.05] [13]. The non-significant difference between the two groups may be due to the small sample size of the population. In a recent study using MIP to indicate DD, Medrinal and co-workers reported that the one-year mortality rate was 31% in patients with low MIP (≤ 30 cmH_2O) versus 7% in patients with high MIP (>30 cmH_2o) [35]. The use of MIP to evaluate DD in the ICU is controversial, as it has a specificity of only 50% for predicting extubation outcome, particularly in patients who exhibit a MIP in a range from less than -20 to -30 cmH_2O [36-38]. Furthermore, Medrinal et al. [35] did not report data on patient MIP prior to admission and did not identify the causes of mortality [35].

For the prediction of weaning outcome, we showed that a Rt. DE of 14 mm [area under the ROC (AUC) of 0.82] was the best cut-off points for predicting weaning failure. Kim et al. [13] reported the same cut-off value (AUC 0.61); however, Lerolle's cut-off was 25 mm for both sides [27]. In the present study, Spont MinVent was significantly higher in the NDD group than in the DD group (12.35 ± 4.22 l/min *vs.* 9.45 ± 2.28 l/min, respectively; p=0.017). Giovanni et al. [10] showed that diaphragmatic thickness was positively correlated with expiratory tidal volume (rho=0.55, p<0.001), which is in partial agreement with our DE findings considering that minute volume (=RR×Vt) [10].

Volumetric weaning parameter (like the RSBI) measures the change in volume generated by the respiratory muscles as a whole rather than that generated by the diaphragm alone. In this regard, RSBI, although easy to obtain, carries an inherent limitation and does not fully reflect the functional state of this principal respiratory muscle [13]. Our study is in agreement regarding the use of diaphragmatic US as a morphometric index for weaning that shows a promising advantage over traditional volumetric indices.

Limitations

US performance by a single physician may be associated with intra- and inter-observer variability in assessing the diaphragm. In subjects with marked DE, the descending lung obscured the diaphragm during deep breathing. Other parameters of diaphragmatic function were not measured, including trans-diaphragmatic pressure, phrenic nerve stimulation and fluoroscopy.

Conclusion

VIDD is present in nearly half of our medical ICU subjects undergoing SBT after mechanical ventilation ≥ 72 h. VIDD is associated with lower DE and longer weaning time. DE being a morphometric index may serve as a valuable tool for predicting weaning outcome as traditional volumetric respiratory indices.

Declarations

Ethics approval and consent to participate: The study was approved by the ethics committee of Cairo University and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The patients' next of kin or legal guardians signed informed consent documents to participate in this study involving human participants

Consent for publication: The patients' next of kin or legal guardians signed an informed consent document permitting the publication and reporting of participating patient data in any form.

Availability of data and material are available inside the master thesis programs of Cairo University.

Competing interests: No potential conflicts of interest exist. The authors have nothing to disclose and declare no conflicts of interest and no relationship with any industry.

Funding: The study was fully funded by Cairo University.

Acknowledgements

We acknowledge all personnel at the radiology department of our institution for their help in facilitating ultrasound use in the ICU.

Trial Registration: The study was registered as a thesis in partial fulfilment of Master's degree at Cairo University from Jan 2014 until May 2017. The study was conducted in the Critical Care Department of Cairo University Hospital.

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