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Can early diaphragm dysfunction in critically ill ventilated patients predict clinical outcomes? A pilot study

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Abstract

Aim: Diaphragm dysfunction (DD) is a keystone factor in difficult weaning from invasive mechanical ventilation (IMV). Diaphragm ultrasound (DUS) is the preferred method for the evaluation of diaphragm function in the Intensive Care Unit (ICU) setting, namely through the diaphragm thickening fraction (DTF). However, its potential role in the decision-making process of mechanical ventilation weaning is yet to be established. We aimed to assess the incidence of early DD and its role as a predictor of prolonged IMV. **Material and methods:** We conducted a prospective, non-interventional study in a university hospital ICU. Non-consecutive adult patients subject to at least 48h of IMV were enrolled. Exclusion criteria was a prior period of IMV in the past three months. DUS was performed at 48h of IMV. End-inspiratory and end-expiratory diaphragm thickness were measured using M-mode, with a high-frequency linear probe placed at the zone of apposition of the diaphragm. The mean values of three measurements were used to calculate DTF. Interobserver measurement variability was not evaluated. **Results:** Forty-five patients were included. Thirty-eight percent were female, average age was 62.3 years. Mean Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) at admission were 50.9 and 9.02, respectively. Mean DTF was 23.46%±17.15. Average IMV duration was 9.36±7.66 days. Half of patients had DD at 48h of IMV. A weak negative correlation was observed between DTF, days of endotracheal intubation (Sp -0.27; p=0.07) and days of IMV (Sp -0.25; p=0.09). Using DTF cut-off values of 20% and 30%, DTF at 48h of IMV was not associated with prolonged IMV (p-values 0.17 and 0.58, respectively). **Conclusion:** In our study, there was a high prevalence of DD at 48h of IMV, as suggested in previous literature. Diaphragm dysfunction at 48h when measured through DTF did not seem to predict prolonged IMV. Late VAP incidence was associated with DD. Diaphragm ultrasound is well-established for diaphragm functional assessment, but further research regarding its trajectory during critical illness is needed to clarify its application in clinical practice.

Keywords: diaphragm thickening fraction; diaphragm dysfunction; invasive mechanical ventilation; ultrasound

Introduction

Atrophy and loss of diaphragm contraction related to invasive mechanical ventilation (IMV) characterize ventilator-induced diaphragm dysfunction (VIDD) [1-3]. It is a highly prevalent cause of poor clinical outcomes, namely prolonged ventilator dependence and associated complications (atelectasis, pneumonia, need for a tracheostomy), and increased overall mortality [4,5].

Since VIDD was first defined by Vassilakopoulos et al 2004 [6], accumulating evidence has shown that it is a keystone factor in difficult weaning from IMV [7,8]. Even after short periods of IMV, muscle unloading and inactivity have deleterious effects on diaphragm contractility [9,10]. As such, there is a great interest in investigating whether the time in which the diagnosis of diaphragm dysfunction (DD) is made can predict the appropriate timing for successful extubation or need for medical interventions.

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Diaphragm ultrasound is a relatively recent, non-invasive and easily available bedside technique that allows for the assessment of diaphragm function by determining certain parameters, such as the diaphragm thickening fraction (DTF), thickness and excursion [3,11,12]. There are several reports in literature of how a reduced DTF (with cut-off values ranging from 20-36%) is associated with failed weaning from IMV, thus revealing its potential as a useful index in the decision-making process of extubating a patient [13-15].

Most of these studies focus on the impact of DTF measured just before or during spontaneous breathing trials (SBTs). Given that VIDD has been proven to be an early phenomenon, it is currently unknown whether it is possible to establish if a prior evaluation of DTF can reliably predict significant clinical outcomes during the rest of the intensive care unit (ICU) stay. Prompt identification of who is likely to require prolonged periods of IMV has proven to be difficult and dependent on numerous factors, as there is a lack of early robust clinical predictors which allow for an individualized approach. Therefore, the aim of this study is to determine if early DD, assessed through DTF, may help predict longer periods of IMV. Moreover, as prolonged ventilator dependence is known to be associated with difficult weaning, it allows us to infer the role of DTF in predicting extubation outcomes.

Material and methods

This prospective, non-interventional study was conducted in a tertiary university hospital in a 34-bed ICU of a multidisciplinary department, located in Lisbon, Portugal, where non-consecutive patients were included during the course of 11 months. The study protocol was approved by the Ethical Commission and informed consent was waived, given the non-interventional design.

Adult patients (age equal or superior to 18 years) subject to 48h of IMV were consecutively enrolled in this study. Exclusion criteria were: a previous period of IMV in the past 3 months, extubation within the first 48h of ICU admission and previously tracheostomized patients.

The main objective was to evaluate DTF at 48h of IMV as a predictor of prolonged IMV. The secondary objectives were to measure the effect of DTF at 48h of IMV as a predictor of ICU length of stay (LOS), re-intubation within 48h and mortality, as well as the effect of diaphragm excursion as a predictor of total IMV time.

We collected clinical data, namely LOS, total IMV time, clinical outcome (mortality), need of re-intubation within 48 hours, diagnosis at ICU admission, age, body max index (BMI), SOFA and SAPS II scores. To access possible cofounders of DD, we also collected data on neuromuscular blockage, ICU acquired weakness (ICUAW) and corticosteroid use. Ultrasound measurements [end-inspiratory thickness (ThI), end-expiratory thickness (ThE), diaphragm excursion (DE)] were recorded.

Diaphragm ultrasounds were performed by 2 senior intensivists, trained in thoracic and diaphragm ultrasound, with Cannon Aplio 300® equipment. A linear probe (Cannon PLT-704SBT model, 4.8-11 MHz frequency) was used for the measurement of the DTF. When assessing DTF, the probe was positioned in a cranio-caudal direction, in the mid-axillary or anterior axillary line, between the 8th and the 10th intercostal spaces. The diaphragm was identified as a hypoechoic band between the parietal pleura (upper hyperechoic line) and peritoneum (inferior hyperechoic line), with a tendinous layer of striated muscle (hyperechoic line) in the middle [16,17]. The probe was positioned perpendicularly to the orientation of the diaphragm and motion mode (M mode) was used to quantify ThI and ThE of the diaphragm. Measurements were repeated in 3 ventilatory cycles in every patient and the mean values of each measurement were used to determine DTF% [(ThI – ThE)/ThE x 100] [18-20]. Measurements were made in the right hemidiaphragm, as the liver provides a more appropriate acoustic window for the accurate assessment of diaphragm thickness [17] and left hemidiaphragm measurements have been reported to be less reproducible [21]. As diaphragm excursion should only be assessed during unassisted breathing, measurements were only performed when a spontaneous breathing trial was possible.

Statistical analysis

Data were analyzed using STATA13.0 (Stata Corporation, College Station, TX, USA). Spearman correlation was used to compare correlation between continuous variables. Chi-squared test and Mann-Whitney U test were used to perform the statistical analysis for categorical and continuous variables, respectively. Diaphragm thickening fraction cut-offs of 20% and 30% were analyzed as a marker of DD. A subgroup analysis was done excluding patients who were deceased 96h after admission, in an attempt to minimize the influence of factors non-related to diaphragm function in IMV time, since a significant number of patients in this study were admitted to the ICU due to cardiorespiratory arrest.

Results

Forty-five patients were included in this study; 17 (37.8%) were female, and the mean age was 62.3±15.0 years old. The majority of the patients were admitted due to medical reasons (66.7%). Mean SOFA at admission and SAPS II scores were 9.0±9.4 and 50.9±18.8. Mean ICU LOS was 14.1±11.8 days. ICU mortality was 33.3%, with a hospital mortality of 40.0% (Table I).

Mean IMV ventilation and endotracheal intubation (ETI) duration were 9.4±7.7 and 8.0±5.5 days, respectively. Two patients were reintubated within 48h. Mean DTF measured at 48h of IMV was 23.5±17.2%. Fifty-one percent of patients had DD at 48h of IMV (Table II).

Using Spearman correlation analysis for the primary outcome, a weak negative correlation was observed between DTF, days of IMV (Sp -0.25; p=0.09) and days of ETI (Sp -0.27; p=0.07) (Table III, fig 1, fig 2). Additionally, there was also a very weak correlation between DTF and ICU LOS (Sp -0.08; p=0.56).

Regarding secondary outcomes, there was no statistically significant association between DTF < 20% and ICU LOS, reintubation at 48h and mortality (ICU and hospital) (Table III).

Using DTF cut-off values of 20% and 30%, DTF at 48h was not associated with prolonged IMV (p-value of 0.17 and 0.58, respectively).

No difference was achieved with subgroup analysis (n=22), excluding patients who were deceased 96h after admission.

Patients with DTF lower than 20% presented a higher risk of late-onset VAP (p=0.04). No statistically significant association was found between DTF <20% and other complications of prolonged IMV (ICUAW or need for tracheostomy), nor with factors such as use of corticosteroids and neuromuscular blockers (Table IV).

Only a reduced number of patients were able to undergo a spontaneous breathing trial (n=5). Therefore, the correlation between DE and IMV days was not determined.

Discussion

In this prospective cohort exploratory study, we found that DD was present in half of the patients after only 48 hours of IMV. No association was found between a reduced DTF and prolonged IMV duration. DTF lower than 20% at 48 hours of IMV was not associated with unfavourable clinical outcomes, such as mortality, ICU LOS and reintubation at 48h. According to our data, patients with a DTF <20% at an early stage

Table I. Demographic description of the population.

Parameter	Summary Data
Gender	
Male	28 (62.2)
Female	17 (37.8)
Age (years old)	62.3±15.0
BMI (Kg/m^2)	27.6±7.0
Motive for admission	
Medical	30 (66.7)
Urgent Surgical	8 (17.8)
Elective Surgical	1 (2.2)
US Trauma	3 (6.7)
ES Trauma	0 (0)
Medical Trauma	3 (6.7)
Coronary	0 (0)
SOFA at admission (points)	9.0±9.4
SAPS II (points)	50.9±18.8
Mortality	
ICU	15 (33.3)
Hospital	30 (40)
ICU Length of stay (days)	14.1±11.8
Use of corticosteroids	21 (46.7)
NMB	13 (28.9)
Hours	9.5±22.2
VAP	
early-onset	1 (2.2)
late-onset	4 (8.9)
Tracheostomy	13 (28.9)

The results are expressed as number (percentage) or mean±standard deviation. BMI – Body Mass Index; US – Urgent Surgical; ES – Elective surgical; SOFA – Sequential Organ Failure Assessment; SAPS – Simplified Acute Physiology Score; ICU – Intensive Care Unit; NMB – Neuromuscular blockers; VAP – Ventilator associated pneumonia

Table II. Ventilation, intubation and ecographic data description.

Parameter	
IMV duration (days)	9.4±7.7
ETI duration (days)	8.0±5.5
Reintubation at 48h	2 (4.4)
Minimum P/F ratio (mmHg)	207.2±87.3
DTF (%)	23.5±17.2
ThI (mm)	2.6±0.9
ThE (mm)	2.2±0.8

The results are expressed as number (percentage) or mean±standard deviation. IMV – Invasive mechanical ventilation; ETI – endotracheal intubation; DTF – Diaphragm thickening fraction; ThI – End-inspiratory thickness; ThE – End-expiratory thickness

Table III. Relation between DTF <20% and secondary outcomes (ICU LOS, reintubation at 48h and mortality).

	ICU LOS	Reintubation at 48h	ICU Mortality	Hospital mortality
DTF <20% (n=23)	12.8±10.1 IQR = [7;16]	1 (4.3%)	5 (21.7%)	7 (30.4%)
DTF >20% (n=22)	15.5±13.5 IQR = [10;48]	1 (4.5%)	10 (45.5%)	11 (50%)
p-value	0.78	0.97	0.09	0.18

DTF – Diaphragm thickening fraction; ICU – Intensive Care Unit; LOS – Length of stay (days); IQR – Interquartile range.

Table IV. Relation between DTF < 20% and complications of prolonged IMV (ICUAW, need for tracheostomy and late-onset VAP), use of corticosteroids and neuromuscular blockers.

	ICUAW	Tracheostomy	Late-onset VAP	CS	NMB
DTF <20% (n=23)	7 (30.4)	5 (21.7)	4 (17.4)	10 (43.5)	6 (26.1)
DTF >20% (n=22)	6 (27.3)	8 (36.4)	0 (0.0)	11 (50.0)	7 (31.8)
p-value	0.82	0.28	0.04	0.66	0.67

The results are expressed as number (percentage). CS – Corticosteroids; DTF – Diaphragm thickening fraction; VAP – Ventilator-associated pneumonia; NMB – Neuromuscular blockers

of IMV seem to be more prone to developing late-onset VAP, a well-known complication of prolonged periods of IMV.

Early DD has a high incidence in critically ill patients, with reports of it being as frequent as 64% in mechanically ventilated patients, within 24 hours of ICU admission [22,23]. In patients experiencing a difficult weaning process or requiring prolonged periods of IMV, this number can rise to 80% [21]. The prevalence of DD varies according to the method employed to assess diaphragm function, as well as the timing of the evaluation itself. Regarding the ultrasonographic-based definition of DD, Kim et al register a 29% prevalence of this condition during the first SBT [8]. In patients requiring more than 7 days of weaning after the first SBT or with ≥3 SBTs, Lu et al identified a 34% prevalence of DD [24]. Our study shows that, at an early stage of IMV, approximately half of the patients had DD, diagnosed by a DTF <20%. This finding corroborates not only the high prevalence of DD, but also the occurrence of an early compromise of diaphragm function in this population.

Most of the published work on the usefulness of DTF in the extubation process suggests that it can successfully predict weaning failure, with cut-off values ranging from 20-36%. This wide range of values can be explained by the variation in the primary outcome [14], as well as measurement of DTF in patients subject to different levels of ventilatory support [15]. DiNino et al determined the DTF of patients during spontaneous breathing trials (SBTs) or pressure support (PS) trials with low levels of support (PS of Δ5/5). They found that a DTF ≥30% was a good predictor of successful extubation with a positive predictive value (PPV) of 0.91 [25]. Blumhof et al documented similar results, with a DTF cut-off value of 20%, even when incrementing PS during an SBT to levels as high as Δ10/5 [26]. Likewise, Ferrari et al registered that a DTF >36% was associated with a successful SBT, with a PPV of 0.92 [27]. All of these studies included reintubation within 48h in the definition of weaning failure.

Goligher et al described those patients with DTF values similar to healthy subjects at rest, during the first three days of ventilation, had the shortest IMV time and ICU length of stay [28]. Dubé et al showed that a DTF

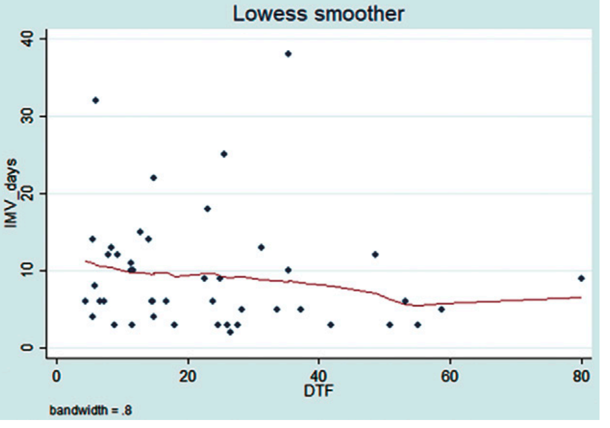

Fig 1. Distribution between diaphragm thickening fraction (DTF) and days of invasive mechanical ventilation (IMV)

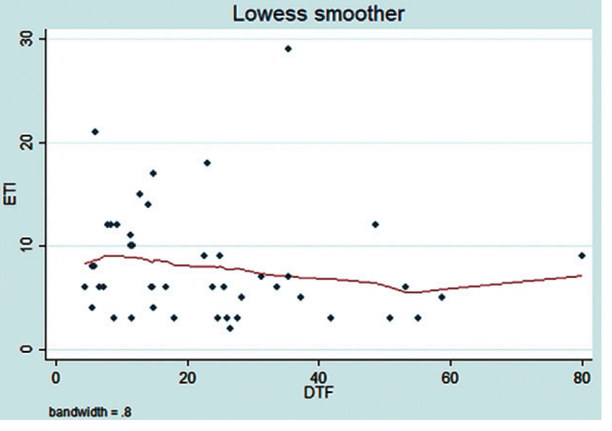

Fig 2. Distribution between diaphragm thickening fraction (DTF) and days of endotracheal intubation (ETI)

<29%, measured at the time of switch to pressure support ventilation, was associated with unfavorable outcomes, such as total duration of IMV, ICU length of stay and mortality [29]. Kim et al found that ICU and hospital length of stay were longer in patients with DD, defined as an excursion <10 mm or paradoxical diaphragm movements, at the time of the first SBT [8]. Although Demoule et al described that ICU mortality was higher among patients with DD, they also found that early DD did not seem to be associated with longer duration of IMV or ICU length of stay [5]. In the present study, early

DD was not associated with more prolonged IMV time, when considering DTF cut-off values of 20% and 30%. Furthermore, mortality, ICU length of stay and need for reintubation within 48h of extubation were not increased in patients with early DD. However, we found that late-onset VAP incidence was higher in patients with early DD, diagnosed by a DTF lower than 20%. It is possible that this association can be indirectly explained by prolonged mechanical ventilation, reduced thoracic expansion and difficult secretion mobilization in patients with DD. Nonetheless, as this condition is known to be linked to longer periods of IMV, we suggest that this finding can potentially indicate a role for DTF in predicting complications related to prolonged ventilator dependence.

One of the main limitations of our study is its reduced sample size and monocentric design with non-consecutive patients. Moreover, the study has methodological flaws, namely the absence of a clear sample size calculation. Another known limitation is the fact that diaphragm ultrasound is an operator-dependent technique. To minimize the influence of interobserver variability, ultrasounds were performed exclusively by 2 senior intensivists. The absence of a consensual definition for weaning failure is a commonly cited limitation in papers on this topic. Although our choice of primary outcome bypasses this problem, it is not without its own shortcomings, as several confounding factors unrelated to diaphragm function can affect the total IMV time. Their influence is mitigated in studies with patients who have either passed or are going through a SBT. Therefore, we deem this to be a relevant limitation of our study. We sought to explore the applicability of DTF as an independent predictor of clinical outcomes in a heterogeneous cohort of severe critically ill patients, when other factors come into play and without disproving the impact of early DD in clinical outcomes. However, our data do not support that early DD, diagnosed by DTF at 48h post-intubation, could be used as an independent predictor of prolonged IMV. This can be the case owing to the existence of multiple additional factors that influence IMV duration or due to the timing of the evaluation itself. Serial assessment of DTF could be a more suitable way of using this index, reflecting changes in diaphragm function during the course of ventilation, as opposed to a single early measurement.

Conclusion

In summary, our study shows that there is a high prevalence of early DD in mechanically ventilated patients. Early DD diagnosed through DTF did not prove to be a reliable independent predictor of poor clinical outcomes. However, late-onset VAP was more frequent in patients with DD, a previously unreported association between DTF and a known complication of prolonged ventilator dependence. Even though ultrasound is a well-established method for functional assessment of the diaphragm, further research including more patients and standardized definitions is required to clarify its applications in clinical practice.

Conflict of interest: none

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