Diaphragmatic Kinetics Assessment by Tissue Doppler Imaging and Extubation Outcome

Gianmaria Cammarota, Ester Boniolo, Erminio Santangelo, Nello De Vita, Federico Verdina,
Samuele Crudo, Ilaria Sguazzotti, Raffaella Perucca, Antonio Messina, Marta Zanoni,
Danila Azzolina, Paolo Navalesi, Federico Longhini, Luigi Vetrugno, Elena Bignami,
Francesco della Corte, Riccardo Tarquini, Edoardo De Robertis, and Rosanna Vaschetto

BACKGROUND: The assessment of diaphragmatic kinetics through tissue Doppler imaging (dTDI) was recently proposed as a means to describe diaphragmatic activity in both healthy individuals and intubated patients undergoing weaning from mechanical ventilation. Our primary aim was to investigate whether the diaphragmatic excursion velocity measured with dTDI at the end of a spontaneous breathing trial (SBT) was different in subjects successfully extubated versus those who passed the trial but exhibited extubation failure within 48 h after extubation. METHODS: We enrolled 100 adult subjects, all of whom had successfully passed a 30-min SBT conducted in CPAP of 5 cm H_2O. In cases of extubation failure within 48 h after liberation from invasive mechanical ventilation, subjects were re-intubated or supported through noninvasive ventilation. dTDI was performed at the end of the SBT to assess excursion, velocity, and acceleration. RESULTS: Extubation was successful in 79 subjects, whereas it failed in 21 subjects. The median (interquartile range [IQR]) inspiratory peak excursion velocity (3.1 [IQR 2.0–4.3] vs 1.8 [1.3–2.6] cm/s, P < .001), mean velocity (1.6 [IQR 1.2–2.4] vs 1.1 [IQR 0.8–1.4] cm/s, P < .001), and acceleration (8.8 [IQR 5.0–17.8] vs 4.2 [IQR 2.4–8.0] cm/s², P = .002) were all significantly higher in subjects who failed extubation compared with those who were successfully extubated. Similarly, the median expiratory peak relaxation velocity (2.6 [IQR 1.9–4.5] vs 1.8 [IQR 1.2–2.5] cm/s, P < .001), mean velocity (1.1 [IQR 0.7–1.7] vs 0.9 [IQR 0.6–1.0] cm/s, P = .002), and acceleration (11.2 [IQR 9.1–19.0] vs 7.1 [IQR 4.6–12.0] cm/s², P = .004) were also higher in the subjects who failed extubation. CONCLUSIONS: In our setting, at the end of SBT, subjects who developed extubation failure within 48 h after extubation experienced a greater diaphragmatic activation compared with subjects who were successfully extubated. (ClinicalTrials.gov registration NCT03962322.) *Key words: diaphragm; Doppler tissue imaging; mechanical ventilator weaning.* [Respir Care 2021;66(6):983–993. © 2021 Daedalus Enterprises]

Introduction

Invasive mechanical ventilation is a lifesaving therapy in critically ill patients. After recovery from the acute phase of illness, a spontaneous breathing trial (SBT) is commonly performed to ascertain whether mechanical ventilation can be withdrawn and the patient extubated.[1] The reported rates of extubation failure range between 10% and 25%, reflecting the variety in causes that may lead to failed extubation.[2] Unfortunately, the failure of a planned extubation is associated with worse outcomes and increased mortality.[3,4] Thus, identifying patients with a high risk for extubation failure is crucial for improving clinical outcome.

Several conditions are associated with extubation failure. The inability to manage tracheobronchial secretions, age > 65 y, and the presence of underlying chronic respiratory or cardiac disease are factors considered to increase the risk of extubation failure.[2,5-11] Additional factors, such as mechanical ventilation ≥ 7 d, delirium, ICU-acquired paresis, acute heart dysfunction, increased rapid shallow breathing index (RSBI), and a positive fluid balance the day before extubation, have been demonstrated to increase the risk of extubation failure.[4,12-15]

Diaphragm ultrasound has been proposed as a technique capable of identifying patients more likely to experience extubation failure after passing an SBT; however, conflicting

results have been reported.[16-18] In addition, the diaphragmatic thickening fraction appears to be a less reliable method for quantifying (in healthy volunteers) diaphragmatic effort.[19,20] Previous data suggest that the displacement velocity of the diaphragm correlates with the extent of muscle activity.[21] Moreover, diaphragmatic tissue Doppler imaging (dTDI) has been recently employed to assess diaphragmatic activity, both in healthy volunteers and in subjects being weaned off invasive mechanical ventilation.[22] However, the potential role of the diaphragmatic excursion kinetics variables (ie, velocity and acceleration) as predictors of extubation failure has never been investigated.

We designed this prospective observational study to test the hypothesis that the sonographic characteristics of diaphragmatic excursion kinetics (ie, velocity and acceleration) assessed through dTDI at the end of an SBT may be different in subjects who go on to be successfully extubated compared with those who exhibit extubation failure. Thus, our primary aim was to evaluate the velocities of diaphragmatic excursion and relaxation, assessed by means of dTDI at the end of the SBT, and to compare the values obtained

Drs Cammarota and De Robertis are affiliated with the Department of Medicine and Surgery, Università degli Studi di Perugia, Perugia, Italy. Drs Boniolo, Santangelo, De Vita, Verdina, Crudo, Azzolina, della Corte, Tarquini, and Vaschetto are affiliated with the Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy. Drs Sguazzotti, Perucca, and Zanoni are affiliated with the Anesthesia and General Intensive Care, Azienda Ospedaliero-Universitaria "Maggiore della Carità", Novara, Italy. Dr Messina is affiliated with the Humanitas Clinical and Research Center – IRCCS, Rozzano, Italy. Dr Navalesi is affiliated with the Department of Medicine, University of Padua, Padua, Italy. Dr Longhini is affiliated with the Department of Medical and Surgical Science, Università Magna Graecia, Catanzaro, Italy. Dr Vetrugno is affiliated with the Department of Medicine, Anesthesia and Intensive Care Clinic, Università di Udine, Udine, Italy. Dr Bignami is affiliated with the Anesthesiology, Critical Care and Pain Medicine Division, Department of Medicine and Surgery, University of Parma, Parma, Italy.

Drs De Robertis and Vaschetto are co-first authors.

Correspondence: Gianmaria Cammarota MD PhD, Department of Medicine and Surgery, Università degli Studi di Perugia, Perugia, Italy. E-mail: gmcamma@gmail.com.

QUICK LOOK

Current knowledge

Diaphragm ultrasound has been proposed as a technique capable of identifying patients more likely to experience extubation failure after passing a spontaneous breathing trial, though there are conflicting results. Diaphragmatic tissue Doppler imaging has been utilized recently to assess diaphragmatic activity, both in healthy volunteers and in individuals being weaned from invasive mechanical ventilation.

What this paper contributes to our knowledge

Diaphragmatic excursion kinetics assessed with tissue Doppler imaging has the potential role to predict extubation failure as early as at the end of a spontaneous breathing trial. In particular, inspiratory peak and mean velocity, in combination with other well-defined risk factors for extubation failure, might play an important role in identifying subjects at risk of re-intubation within 48 h after extubation. Greater diaphragmatic activation was associated with extubation failure.

in individuals successfully extubated with those of subjects exhibiting extubation failure within 48 h after withdrawal of invasive mechanical ventilation. Secondarily, we aimed to ascertain whether the variables assessed with dTDI can be used to predict extubation failure.

Methods

Our observational cohort study, approved by local the ethics committee on March 22, 2019 (CE 23/19) and subsequently registered with ClinicalTrials.gov (NCT03962322) was conducted in accordance with the Helsinki Declaration principles in the ICU of "Maggiore della Carità" University Hospital, Novara, Italy. Written informed consent was obtained from all subjects according to local regulations.

Subjects

Adult patients who had undergone invasive mechanical ventilation for > 24 h and were extubated after passing a 30-min SBT on CPAP of 5 cm H_2O according to our institutional weaning protocol, conducted using the ventilator circuit, were eligible for enrollment (to view our detailed institutional weaning protocol, see the supplementary materials at http://www.rcjournal.com). Exclusion criteria were a failed SBT, a previous diagnosis of diaphragmatic palsy, recent thoracotomy or sternotomy (within the previous year), diagnosis of pneumothorax or pneumomediastinum,

consent refusal, a poor diaphragmatic ultrasound window, pregnancy, and end-of-life extubation.

Ultrasound

dTDI measurements were obtained at the bedside with subjects in a 30° semi-recumbent position using a portable ultrasound machine equipped with a sectorial probe (1.8–4.2 MHz) and a dedicated cardiac tissue Doppler application (Xario 200, Canon Medical Systems, Zoetermeer, The Netherlands).[22,23] Using the right side only (due to the poor acoustic window of the left side resulting from the presence of the spleen and impairments deriving from gastric or colic meteorism[24,25]), the transducer was positioned between the midclavicular and anterior axillary line in the subcostal region and oriented to find the confluence of the hepatic veins into the inferior vena cava via the liver.[23,26,27] With the ultrasound beam perpendicularly oriented toward the middle or posterior third of the diaphragm, the tissue Doppler application was switched on and a clear diaphragm signal was attained by gain fading and excluding high-frequency signals. Once the Doppler cursor had been aligned to the diaphragmatic displacement direction, the maximum amplitude sample box (20 mm) was positioned on the diaphragmatic line to acquire its excursion.[22,23] The velocity scale was set as low as possible to catch the slower velocity of diaphragmatic excursion with respect to the beating heart (Fig. 1A).[22] From the dTDI waveforms, the following parameters were acquired (Fig. 1B): inspiratory peak velocity (the maximum velocity during inspiration; cm/s), inspiratory mean velocity (the mean velocity computed across the whole inspiration; cm/s), velocity-time integral (excursion) (the area under the velocity curve for the entire inspiration; cm), inspiratory acceleration (the slope of the steepest portion of the inspiratory velocity curve from baseline to inspiratory peak velocity; cm/s^2), peak relaxation velocity (the maximum diaphragmatic velocity during expiration; cm/s), expiratory mean velocity (the mean velocity computed over the full expiration; cm/s), and expiratory acceleration (relaxation rate) (the slope of the steepest portion of the expiratory velocity curve from baseline to peak relaxation velocity; cm/s^2). The values of these parameters were averaged for 3 consecutive breaths and stored electronically.

Protocol

dTDI was performed by a single operator, who was not involved in the subjects' care, at the end of the SBT. After extubation, subjects were allowed to breathe spontaneously with additional oxygen to maintain S_{pO_2} between 90% and 94%. Subjects at high risk for extubation failure subsequently received noninvasive ventilation (NIV), either in CPAP or pressure support ventilation mode.[28,29] Extubation failure was defined as the need for re-intubation or NIV as a rescue therapy within 48 h after extubation[29,30] (for NIV application and re-intubation criteria in the case of extubation failure, see the supplementary materials at http://www.rcjournal.com). Subjects receiving prophylactic NIV or high-flow nasal cannula were not considered as extubation failures.

Measurements

Subject demographics, admission diagnosis, and Simplified Acute Physiologic Score II (SAPS II) were acquired for all individuals. S_{pO_2}, electrocardiogram, invasive arterial blood pressure, breathing frequency, and tidal volume were monitored throughout the whole study period. dTDI evaluation, arterial blood gas analysis, assessment of dyspnea according to the visual analog scale, and sedation according to Richmond Agitation-Sedation Scale (RASS) were obtained immediately after the end of the SBT. The tidal volume and breathing frequency were acquired from the ventilator. Furthermore, conventional and diaphragmatic RSBIs were computed as previously described.[24,31]

Intra- and Inter-Observer Reliability dTDI intra- and inter-observer reliability of 2 operators were tested prior to subject enrollment. Each assessor carried out dTDI evaluations in 10 intubated ICU individuals. For each subject, the dTDI measurements were acquired across 4 breaths. Five minutes after the completion of the first assessment, a second dTDI assessment was performed in the same subject for another 4 breaths.

Statistical Analysis The sample size was computed based on the difference in diaphragmatic peak relaxation velocity between successfully weaned subjects and those who experienced weaning failures, according to recent findings.[22] In our setting, the subjects enrolled in the study were divided in 2 groups: extubation failures and extubation successes. Considering an expected extubation failure rate of 20%,[2] a total of 89 subjects were calculated as necessary to demonstrate whether any difference in diaphragmatic peak relaxation velocity existed between extubation failure subjects and extubation success subjects (Type I error rate = 0.05; Type II error rate = 0.20, 80% power). Assuming a 10% dropout rate, we opted for a sample size of 100 subjects.

Data are summarized as medians (interquartile range) and were analyzed using the Mann-Whitney test for the comparison of continuous variables between the extubation failure group and the extubation success group. Categorical variables, whenever dichotomous or nominal, were reported as numbers and percentages and analyzed using the Fisher exact test. Receiver operating characteristic curves were also obtained for dTDI parameters, as well as for the conventional and diaphragmatic RSBIs. The area
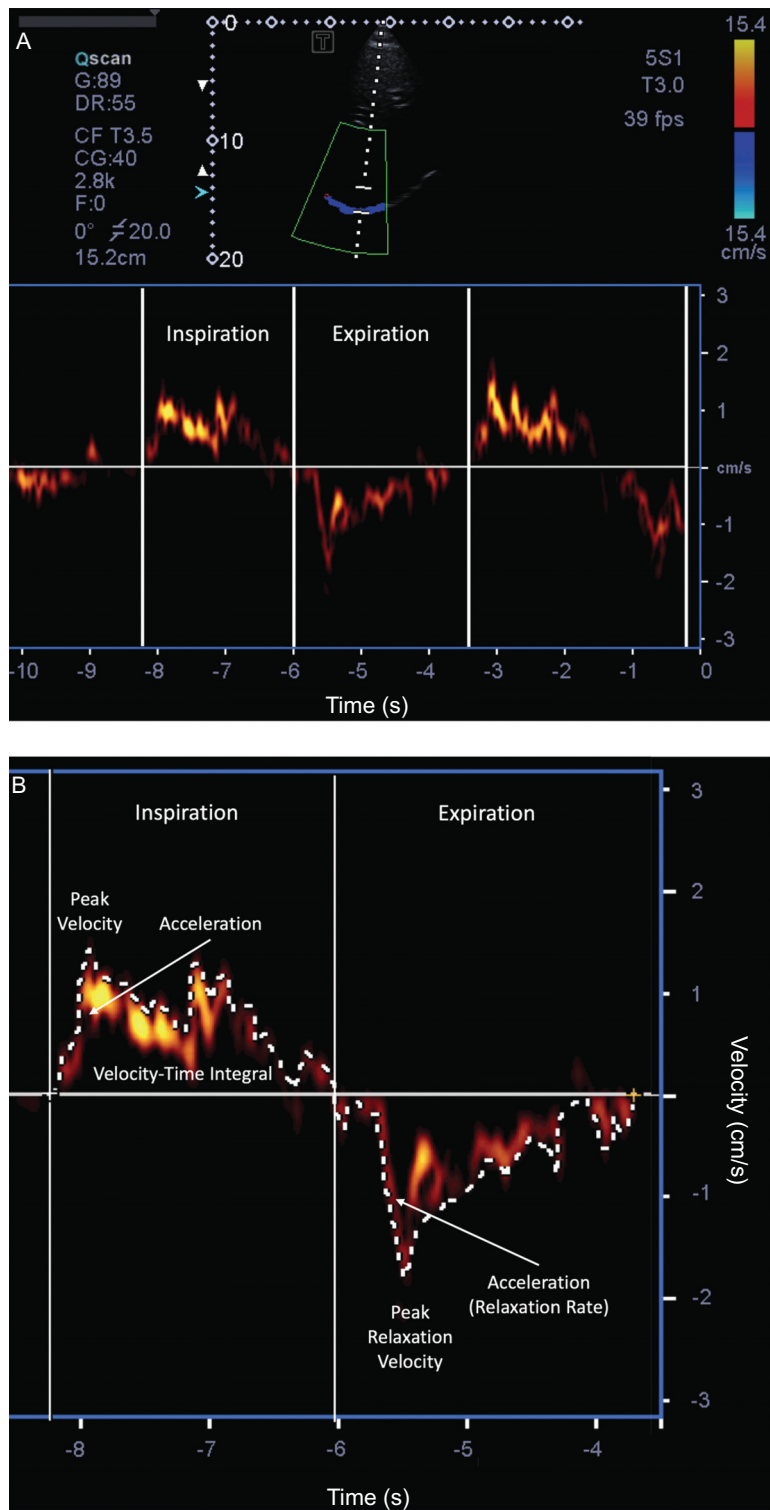
Fig. 1. Diaphragmatic excursion velocity assessment through tissue Doppler imaging. The spectrum of diaphragmatic excursion velocity is reported during inspiration and expiration. A: Diaphragmatic kinetics variables during inspiration and expiration. B: Inspiratory peak velocity = the maximal velocity during inspiration (cm/s); inspiratory mean velocity = the mean velocity computed across the whole inspiration (cm/s); velocity-time integral (excursion) = the area under the velocity curve for the entire inspiration (cm); inspiratory acceleration = the slope of the steepest portion of the inspiratory velocity curve from baseline to inspiratory peak velocity (cm/s^2); peak relaxation velocity = the maximum diaphragmatic velocity during expiration (cm/s); expiratory mean velocity = the mean velocity computed over the full expiration (cm/s); expiratory acceleration (relaxation rate) = the slope of the steepest portion of the expiratory velocity curve from baseline to peak relaxation velocity (cm/s^2).

under the curve, cutoff, sensitivity, specificity, and positive and negative likelihood ratios were reported for tissue Doppler parameters and for conventional and diaphragmatic RSBIs. Area under the curve comparisons were carried out according to the DeLong method.[32] Two-tailed tests were applied for hypothesis testing, and statistical significance was considered for P values $< .05$.

For the dTDI intra- and inter-observer reliability analysis, Pearson correlation, bias with the limits of agreement, and the intraclass correlation coefficient were computed. For computation of the intraclass correlation coefficient, 2-way mixed effects for absolute agreement between the measurements for each dTDI variable were considered.[33] Statistical analyses were conducted using R 3.5.2 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

As depicted in Figure 2, from May to November 2019, 159 subjects were assessed for eligibility, of whom 100 subjects were enrolled and finally analyzed (ie, 79 extubation success subjects and 21 extubation failure subjects). The causes of postextubation respiratory failure were inspiratory stridor in 3 of 21 subjects (14.3%), respiratory failure in 10 of 21 subjects (47.6%), cardiac arrest in 1 of 21 subjects (4.8%), and neurological impairment in 7 of 21 subjects (33.3%). Prophylactic NIV was employed in 12 subjects (15.2%) and 5 subjects (23.8%) in the extubation success and failure groups, respectively. The baseline characteristics of the study population are reported in Table 1. Of the admission diagnoses, comorbidities were more frequently observed in the extubation failure group compared with individuals in the extubation success group ($P = .032$). In 7 subjects (33.3%) from the extubation
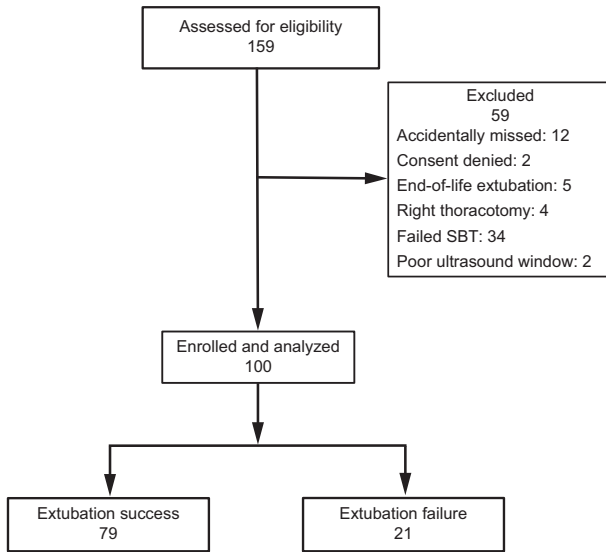

Fig. 2. Flow chart. SBT = spontaneous breathing trial.

Table 1. Baseline Characteristics of the Study Population

Characteristics	Extubation Success (n = 79)	Extubation Failure (n = 21)	P
Male sex, n (%)	42.0 (53.2)	12.0 (57.1)	.81
Age, y	66.0 (52.0–77.0)	66.0 (62.5–73.0)	.31
Body mass index, kg/m^2	24.2 (22.5–26.4)	24.2 (21.8–27.7)	.11
Predicted body weight, kg	64.2 (57.0–68.8)	60.0 (53.8–66.0)	.43
SAPS II at admission	30.0 (24.0–42.0)	39.0 (33.5–46.5)	.02
Ventilation duration before extubation, d	2.0 (1.0–5.0)	3.0 (1.0–7.0)	.61
Pressure support, cm H$_2$O	8.0 (5.0–9.0)	8.0 (6.0–10.0)	.25
PEEP, cm H$_2$O	5.0 (5.0–8.0)	5.0 (5.0–6.0)	.84
Steroids administration	27 (34.2)	8 (38.1)	.80
Myo-relaxant infusion	2 (2.5)	1 (4.8)	.51
Admission diagnosis			
Emergency neurosurgery	11.0 (13.9)	6.0 (28.6)	.19
Elective neurosurgery	14.0 (17.7)	1.0 (4.8)	.18
Respiratory failure	10.0 (12.7)	5.0 (23.8)	.30
Cardiac arrest	2.0 (2.5)	0.0 (0.0)	> .99
Shock	7.0 (8.9)	0.0 (0.0)	.34
Trauma	11.0 (13.9)	2.0 (9.5)	.73
Other surgeries	19.0 (24.1)	2.0 (9.5)	.23
Other diseases	5.0 (6.3)	5.0 (23.8)	.032

Data are presented as n (%) or median (interquartile range). *P* values refers to Fisher exact, chi-square, or Wilcoxon test.
SAPS II = Simplified Acute Physiology Score II

Table 2.   Diaphragmatic Excursion Tissue Doppler at the End of the Spontaneous Breathing Trial

Parameters	Successes	Failures	P
Inspiratory peak velocity, cm/s	1.8 (1.3–2.6)	3.1 (2.0–4.3)	< .001
Inspiratory mean velocity, cm/s	1.1 (0.8–1.4)	1.6 (1.2–2.4)	< .001
Inspiratory acceleration, cm/s^2	4.2 (2.4–8.0)	8.8 (5.0–17.8)	.002
Inspiratory velocity-time integral, cm	1.6 (1.2–2.3)	2.2 (1.6–2.6)	.12
Peak relaxation velocity, cm/s	1.8 (1.2–2.5)	2.6 (1.9–4.5)	< .001
Expiratory mean velocity, cm/s	0.9 (0.6–1.0)	1.1 (0.7–1.7)	.002
Expiratory acceleration, cm/s^2	7.1 (4.6–12.0)	11.2 (9.1–19.0)	.004

Data are presented as median (interquartile range). P values determined with the Mann-Whitney test for comparison between the extubation success and extubation failure groups.

Table 3.   Accuracy in Predicting Extubation Failure at the End of the Spontaneous Breathing Trial

Variable	Area Under the Curve	Standard Error	95% CI	P	Cutoff	Sensitivity	95% CI	Specificity	95% CI	Likelihood Ratio Positive	Likelihood Ratio Negative	DOR	95% CI
Inspiratory peak velocity	0.8	0.1	0.7–0.8	< .001	> 2.2	76.2	52.8–91.8	62.0	5.4–72.7	2.0	0.4	4.1	1.4–11.7
Inspiratory mean velocity	0.8	0.1	0.7–0.8	< .001	> 1.4	71.4	47.8–88.7	77.2	66.4–85.9	3.1	0.4	8.5	2.9–25.0
Inspiratory acceleration	0.7	0.1	0.6–0.8	< .001	> 5.3	76.2	52.8–91.8	64.6	53.0–75.0	2.2	0.4	5.8	1.9–17.6
Expiratory peak velocity	0.7	0.1	0.6–0.8	< .001	> 2.5	57.1	34.0–78.2	78.5	67.8–86.9	2.7	0.6	3.9	1.4–10.7
Expiratory mean velocity	0.7	0.1	0.6–0.8	.02	> 1.2	47.6	25.7–70.2	86.1	76.5–92.8	3.4	0.6	4.6	1.6–13.1
Expiratory acceleration	0.7	0.1	0.6–0.8	.039	> 12.3	57.1	34.0–78.2	78.5	67.8–86.9	2.7	0.6	4.5	1.6–12.4
Conventional RSBI	0.6	0.1	0.5–0.7	.18	> 45.4	57.1	34.0–78.2	63.3	51.7–73.9	1.6	0.7	2.3	0.9–6.1
Diaphragmatic RSBI	0.6	0.1	0.5–0.7	.39	≤ 12.6	76.2	52.8–91.8	45.6	34.3–57.2	1.4	0.5	2.7	0.9–8.0

DOR = diagnostic odds ratio
RSBI = rapid shallow breathing index

failure group, an ineffective cough was described before re-intubation.

In our setting, diaphragmatic excursion kinetics were assessed with dTDI evaluation for a total of 300 breaths (ie, 237 breaths in the extubation success group, 63 breaths in the extubation failure group). Table 2 describes the dTDI assessments at the end of the SBT. Despite no differences in inspiratory excursion observed at the end of the SBT, the inspiratory peak excursion velocity, mean velocity, and acceleration were lower in extubation success subjects compared with those attained from extubation failure subjects. Similarly, during expiration, extubation failure subjects showed a higher peak relaxation velocity, mean velocity, and acceleration compared with those obtained from extubation successes.

Table 3 reports the accuracy with which the dTDI variables and conventional and diaphragmatic RSBIs are able to predict extubation failure at the end of the SBT. The

related receiver operating characteristic curves are depicted in Figure 3 for inspiratory and expiratory diaphragmatic kinetics parameters. The area under the curve values for the inspiratory peak and mean velocities were wider than those obtained for the conventional (vs inspiratory peak velocity, P = .036; vs inspiratory mean velocity, P = .042) and diaphragmatic RSBIs (vs inspiratory peak velocity, P = .01; vs inspiratory mean velocity, P = .005). The comparison of areas under the curve is presented in Table 4.

Table 5 reports subjects' breathing patterns, hemodynamics, visual analog scale dyspnea, and sedation level, as well as the conventional and diaphragmatic RSBI values at the end of the SBT. With the exception of the breathing frequency and visual analog scale dyspnea, which were lower in extubation successes than in extubation failures, no differences in the remaining parameters were observed.
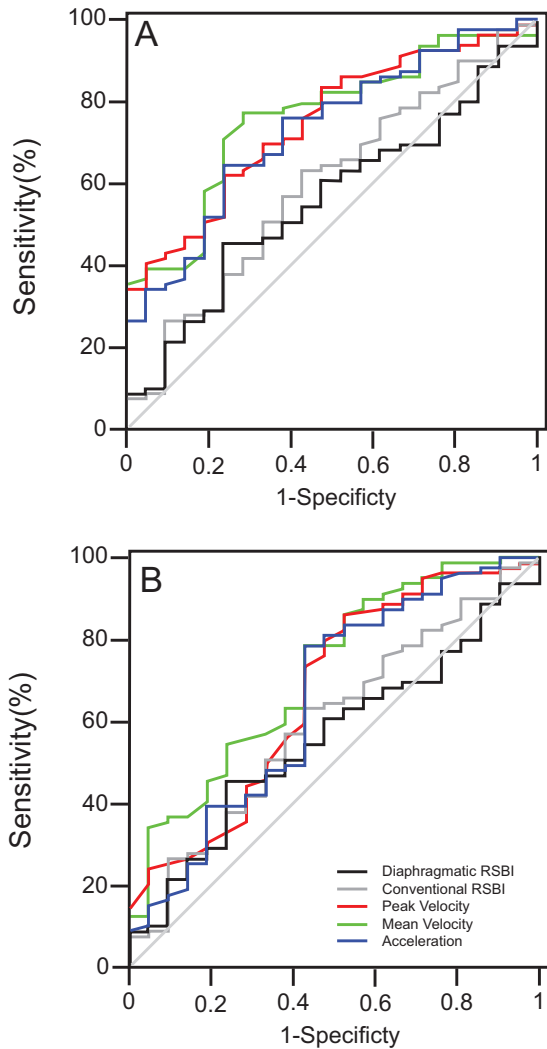
Fig. 3. Receiver operating characteristic curves for diaphragmatic displacement tissue Doppler parameters, conventional and diaphragmatic RSBIs. A: Inspiratory values. B: Expiratory values. RSBI = rapid shallow breathing index; AUC, area under the curve.

Table 4. Difference in Area Under the Curve Analysis

Comparison	Difference in Areas Under the Curve	P
Inspiratory Peak Velocity vs Conventional RSBI	0.15 (0.01–0.29)	.036
Inspiratory Peak Velocity vs Diaphragmatic RSBI	0.19 (0.04–0.34)	.01
Inspiratory Mean Velocity vs Conventional RSBI	0.17 (0.01–0.33)	.042
Inspiratory Mean Velocity vs Diaphragmatic RSBI	0.20 (0.06–0.35)	.005
Inspiratory Acceleration vs Conventional RSBI	0.14 (–0.02 to 0.29)	.09
Inspiratory Acceleration vs Diaphragmatic RSBI	0.017 (–0.07 to 0.10)	.71
Expiratory Peak Velocity vs Conventional RSBI	0.13 (–0.02 to 0.27)	.09
Expiratory Peak Velocity vs Diaphragmatic RSBI	0.16 (–0.00 to 0.33)	.055
Expiratory Mean Velocity vs Conventional RSBI	0.08 (–0.08 to 0.24)	.35
Expiratory Mean Velocity vs Diaphragmatic RSBI	0.11 (–0.05 to 0.28)	.17
Expiratory Acceleration vs Conventional RSBI	0.06 (–0.10 to 0.21)	.46
Expiratory Acceleration vs Diaphragmatic RSBI	0.10 (–0.12 to 0.31)	.38

RSBI = rapid shallow breathing index

The intra-class correlation coefficient was ≥ 0.85 for all dTDI variables.

Discussion

The main findings of this study can be summarized as follows: (1) at the end of the SBT, with the exception of inspiratory excursion, which was similar among groups, all the other dTDI variables were significantly higher in the subjects who went on to exhibit extubation failure within 48 h after invasive mechanical ventilation interruption compared with those who were successfully extubated; (2) in our mixed ICU population, values of diaphragmatic inspiratory peak and mean velocity were good predictors of subsequent extubation failure following a successful SBT; and (3) in this study, dTDI assessment was characterized by good intra- and inter-observer reliability.

Diaphragm ultrasound is an easy-to-learn technique,[34] widely used to monitor mechanical ventilation both in the ICU[20,35] and in the emergency department.[36] However, the role of diaphragm ultrasound in predicting extubation failure is still under debate.[16-18] In a recent study, dTDI was employed at the end of the SBT to evaluate diaphragmatic kinetics during weaning from invasive mechanical

The arterial blood gas data for the study population are presented in Table 6. At the end of the SBT, P_{aO_2}/F_{IO_2} was higher in extubation success subjects than in extubation failure subjects. pH, P_{aCO_2}, lactate, and bicarbonate serum levels were not different between groups.

Clinical outcomes are reported in Table 7. As expected, ICU length of stay, re-intubation rate, and tracheostomy rate were higher in the extubation failure group than in the extubation success group.

For dTDI intra- and inter-observer variability, a total of 160 breaths were analyzed (ie, 80 for each assessor). The Pearson correlation coefficient, the bias with limits of agreement, and the intra-class correlation coefficient for each dTDI variable are presented in the supplementary materials (available at http://www.rcjournal.com).

Table 5. Parameters at the End of the Spontaneous Breathing Trial

Parameters	Successes	Failures	P
Tidal volume, mL	500.0 (405.0–600.0)	450.0 (400.0–530.0)	.59
Breathing frequency, breaths/min	19.0 (14.0–22.0)	22.0 (18.0–24.5)	.047
Mean arterial pressure, mm Hg	90 (82.0–102.0)	100 (82.5–108.5)	.08
Heart rate, beats/min	90.0 (74.0–100.0)	90.0 (77.0–99.0)	.91
Visual analog scale dyspnea score	2.0 (0.0–3.0)	3.0 (0.5–5.0)	.009
RASS score	0 (0–0)	0 (–1.0 to 0.5)	.49
RSBI, breaths/min/L	38.5 (23.9–52.4)	47.4 (29.8–59.0)	.21
Diaphragmatic RSBI, breaths/min/cm	11.5 (6.8–17.7)	9.7 (7.0–14.4)	.27

Data are presented as median (interquartile range). P values determined with the Mann-Whitney test for comparison between the extubation success and extubation failure groups.
RASS = Richmond Agitation-Sedation Scale
RSBI = rapid shallow breathing index

Table 6. Arterial Blood Gases

Parameters	Successes	Failures	P
pH	7.41 (7.36–7.44)	7.43 (7.38–7.48)	.16
P_{aCO_2}, mm Hg	4.7 (36.3–44.4)	42.5 (37.2–46.7)	.18
P_{aO_2}/F_{IO_2}, mm Hg	315.0 (242.0–369.0)	248.0 (189.0–330.0)	.008
Lactate, mmol/L	1.5 (0.9–2.1)	1.1 (0.6–1.9)	.17
Bicarbonate, mmol/L	25.7 (23.5–29.0)	29.2 (23.8–32.6)	.069

Data are presented as median (interquartile range). P values refer to Mann-Whitney test for comparison between extubation success and extubation failure group.

Table 7. Clinical Outcomes

Characteristics	Extubation Success (n = 79)	Extubation Failure (n = 21)	P
Length of ICU stay, d	3.0 (1.0–8.0)	12.0 (5.5–14.0)	< .001
Rate of re-intubation	1.0 (1.3)	13 (61.9)	< .001
Rate of tracheostomy	1.0 (1.3)	7.0 (33.3)	< .001
ICU mortality	3.0 (3.8)	1.0 (4.8)	.99

Data are presented as n (%) and percentage or median (interquartile range). P values refer to chi-square and Wilcoxon tests.

ventilation.[22] According to this previous investigation,[22] inspiratory peak velocity, expiratory relaxation velocity, and expiratory maximum relaxation rate (ie, acceleration) were higher in subjects who failed the SBT with respect to subjects who passed the weaning trial. In good agreement with that study,[22] in our setting, the abovementioned dTDI variables were higher in subjects in the extubation failure group compared with subjects in the extubation success group, with the exception of the inspiratory velocity-time integral (ie, inspiratory excursion). In addition, we observed higher values of mean velocity during both inspiration and expiration as well as inspiratory acceleration in the extubation failure subjects than in extubation success subjects. However, although the values of inspiratory peak velocity and expiratory relaxation velocity in our extubation failure subjects were quite similar to those of the weaning failure group in the study by Soilemezi et al (3.29 vs 2.66 cm/s and 3.26 vs 3.36 cm/s, respectively),[22] the expiratory relaxation rate was substantially lower in our extubation failure subjects compared with the weaning failures from Soilemezi et al (17.59 vs 29.47 cm/s², respectively).[22] This probably depended on the different SBT modes adopted in the 2 studies (ie, CPAP 5 cm H_2O in our study vs T-tube in the cited study[22]) and the fact that, contrary to our subjects who all passed the weaning trial and were extubated, the weaning failure group in the cited study[22] constituted those who did not pass the SBT and continued invasive mechanical ventilation.

Inspiratory diaphragmatic excursion during an assisted breath is the sum of machine ventilatory assistance and diaphragmatic contraction.[35,37] In light of previous findings,[38] we can hypothesize that the extent of inspiratory diaphragmatic activity increased in our subjects when ventilatory support was removed during the SBT. Although the SBT was conducted in CPAP 5 cm H_2O mode in our setting, the higher dTDI parameters at the end of the SBT suggested a greater diaphragmatic activation in extubation failures with respect to extubation successes. The greater diaphragmatic activation observed in extubation failure subjects could be explained by a lower level of oxygenation in these subjects compared with the extubation success group, which may have acted as a continuous trigger for increased respiratory demand.[39,40] The hypothesis that diaphragmatic effort was greater in the extubation failure group to ensure adequate alveolar ventilation and gas exchange is congruent with previous findings obtained in intubated ICU subjects undergoing mechanical ventilation.[41] According to these results,[41] extubation failure subjects experienced poorer outcomes, not only in the presence of diaphragmatic atrophy/failure, but also when the respiratory muscles were not sufficiently unloaded during mechanical ventilation. To note, diaphragmatic dysfunction has been described in

approximatively 40% of patients within the first 3 d of invasive mechanical ventilation.[25,41] This dysfunction is sustained by a reduction in the strength and cross-sectional area of the myofibers as a result of excessive ventilatory assistance, deep sedation, and myo-relaxant administration.[42,43] The extent of diaphragmatic inactivity is correlated to diaphragmatic thickness and is associated with adverse outcome in intubated patients.[44]

In our investigation, dTDI parameters were more accurate predictors of extubation failure than both the conventional[15] and diaphragmatic[24] RSBIs. The conventional RSBI is one of the most-used clinical predictors of weaning and extubation outcome because it provides a good indication of the balance between the mechanical load placed on the respiratory muscles and their ability to handle this load during an SBT performed in T-tube mode.[15,31] However, when an SBT is conducted in modes other than the T-tube mode, the variability in the sensitivity and specificity of this index in predicting weaning outcome is greater.[45] Recently, the diaphragmatic RSBI, which assesses the ratio of diaphragmatic excursion to breathing frequency, has been proposed.[24] Despite being a good predictor of weaning outcome when SBT is conducted using a T-piece, this index might be affected by the same limitations associated with the conventional RSBI during an SBT conducted in pressure support ventilation or CPAP mode. Thus, in our setting, neither the conventional nor the diaphragmatic RSBI provided a satisfactory predictive value with respect to extubation outcome, as expected.

Regarding clinical implications, once a patient has successfully passed an SBT with an increased diaphragmatic activation as revealed by dTDI assessment, close clinical monitoring should be ensured in the 48 h after extubation to enable the prompt identification of the onset of extubation failure and a timely intervention. Alternatively, under these conditions, the application of prophylactic NIV soon after extubation might be justified to reduce the mismatch between the load imposed on the diaphragm and its neuromuscular capacity during spontaneous breathing.

Limitations

Our study has several limitations. First, this was a single-center observational study conducted on a mixed ICU population, including mainly neurocritical care subjects. Despite the number of subjects involved, our findings should be confirmed in further investigations specifically addressing the different subsets of subjects and focused on the validation of the dTDI technique. Second, we employed dTDI at the end of the SBT conducted in CPAP 5 cm H_2O mode. Thus, our conclusions cannot be extended to SBTs carried out in other modalities. Third, we decided a priori not to assess the diaphragmatic thickness and thickening fraction. Indeed,

diaphragmatic thickness and thickening fraction assessment are more prone to intra- and inter-individual errors (ie, parallax error and the capacity to acquire the thickening fraction on the same portion of the diaphragm over time) compared with excursion analysis.[20,46] Moreover, the validity of the diaphragmatic thickening fraction to ascertain diaphragmatic effort is limited because it is only moderately correlated with the pressure-generating capacity of the diaphragm.[19,20] Fourth, we only investigated and reported dTDI evaluations in subjects who passed the SBT because our aim was only to assess the existence of a relationship between postextubation respiratory failure and dTDI variables acquired at the end of an SBT. Last, we defined extubation failure as the need for re-intubation or NIV within 48 h after extubation.[29,30,47] However, our results might be different if the definition were extended to 7 d after extubation, as recently described.[48]

Conclusions

In our mixed ICU population, when dTDI was performed at the end of an SBT, a greater diaphragmatic activation was observed in subjects who experienced extubation failure within 48 h after extubation compared with those who were successfully extubated, with no difference in inspiratory diaphragmatic displacement. Diaphragmatic inspiratory peak and mean velocity performed well as predictors of extubation failure occurring within 48 h of a successful SBT. Our results must be confirmed in future multicenter clinical trials addressing the role of dTDI in the prediction of extubation failure.

REFERENCES

1. Perren A, Brochard L. Managing the apparent and hidden difficulties of weaning from mechanical ventilation. Intensive Care Med 2013;39 (11):1885-1895.
2. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med 2011;39:2612-2618.
3. Torres A, Gatell JM, Aznar E, El-Ebiary M, Puig De La Bellacasa J, González J, et al. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med 1995;152(1):137-141.
4. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. Chest 1997;112(1):186-192.
5. Mokhlesi B, Tulaimat A, Gluckman TJ, Wang Y, Evans AT, Corbridge TC. Predicting extubation failure after successful completion of a spontaneous breathing trial. Respir Care 2007;52:1710-1717.
6. Salam A, Tilluckdharry L, Amoateng-Adjepong Y, Manthous CA. Neurologic status, cough, secretions and extubation outcomes. Intensive Care Med 2004;30(7):1334-1339.

7. Khamiees M, Raju P, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. Chest 2001;120 (4):1262-1270.

8. Smina M, Salam A, Khamiees M, Gada P, Amoateng-Adjepong Y, Manthous CA. Cough peak flows and extubation outcomes. Chest 2003;124(1):262-268.

9. Huang C-T, Yu CJ. Conventional weaning parameters do not predict extubation outcome in intubated subjects requiring prolonged mechanical ventilation. Respir Care 2013;58(8):1307-1314.

10. Vallverdú I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. Am J Respir Crit Care Med 1998;158(6):1855-1862.

11. Namen AM, Ely EW, Tatter SB, Case LD, Lucia MA, Smith A, et al. Predictors of successful extubation in neurosurgical patients. Am J Respir Crit Care Med 2001;163(3):658-664.

12. Thille AW, Boissier F, Ghezala H, Ben Razazi K, Mekontso-Dessap A, Brun-Buisson C. Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study. Crit Care Med 2015;43(3):613-620.

13. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. J Am Med Assoc 2004;291 (14):1753-1762.

14. De Jonghe B, Bastuji-Garin S, Durand MC, Malissin I, Rodrigues P, Cerf C, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med 2007;35:2007-2015.

15. Frutos-Vivar F, Ferguson ND, Esteban A, Epstein SK, Arabi Y, Apezteguía C, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. Chest 2006;130 (6):1664-1671.

16. Farghaly S, Hasan AA. Diaphragm ultrasound as a new method to predict extubation outcome in mechanically ventilated patients. Aust Crit Care 2017;30(1):37-43.

17. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: Influence on weaning from mechanical ventilation. Crit Care Med 2011;39:2627-2630.

18. Vivier E, Muller M, Putegnat JB, Steyer J, Barrau S, Boissier F, et al. Inability of diaphragm ultrasound to predict extubation failure: a multicenter study. Chest 2019;155(6):1131-1139.

19. Oppersma E, Hatam N, Doorduin J, Hoeven JG, Van D, Marx G, Goetzenich A, et al. Functional assessment of the diaphragm by speckle tracking ultrasound during inspiratory loading. J Appl Physiol (1985) 2017;123(5):1063-1070.

20. Goligher EC, Laghi F, Detsky ME, Farias P, Murray A, Brace D, et al. Measuring diaphragm thickness with ultrasound in mechanically ventilated patients: feasibility, reproducibility and validity. Intensive Care Med 2015;41(4):642-649.

21. Ayoub J, Cohendy R, Dauzat M, Targhetta R, La Coussaye J D, Bourgeois JM, et al. Non-invasive quantification of diaphragm kinetics using m-mode sonography. Can J Anaesth 1997;44(7):739-744.

22. Soilemezi E, Savvidou S, Sotiriou P, Smyrniotis D, Tsagourias M, Matamis D. Tissue Doppler imaging of the diaphragm in healthy subjects and critically ill patients. Am J Respir Crit Care Med 2020;202 (7):1005-1053.

23. Cammarota G, Boniolo E, Tarquini R, Vaschetto R. Diaphragmatic excursion tissue Doppler sonographic assessment. Intensive Care Med 2020;46(9):1759-1760.

24. Spadaro S, Grasso S, Mauri T, Dalla Corte F, Alvisi V, Ragazzi R, et al. Can diaphragmatic ultrasonography performed during the T-tube trial predict weaning failure? The role of diaphragmatic rapid shallow breathing index. Crit Care 2016;20(1):305-311.

25. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, et al. Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. Am J Respir Crit Care Med 2015;192 (9):1080-1088.

26. Radicioni M, Rinaldi VE, Camerini PG, Salvatori C, Leonardi A, Bini V. Right diaphragmatic peak motion velocities on pulsed wave tissue Doppler imaging in neonates: method, reproducibility, and reference values. J Ultrasound Med 2019;38(10):2695-2701.

27. Fayssoil A, Nguyen LS, Ogna A, Stojkovic T, Meng P, Mompoint D, et al. Diaphragm sniff ultrasound: normal values, relationship with sniff nasal pressure and accuracy for predicting respiratory involvement in patients with neuromuscular disorders. PLoS One 2019;14(4): e0214288.

28. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50(2):1602426.

29. Renda T, Corrado A, Iskandar G, Pelaia G, Abdalla K, Navalesi P. High-flow nasal oxygen therapy in intensive care and anaesthesia. Br J Anaesth 2018;120(1):18-27.

30. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J 2007;29(5):1033-1056.

31. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med 1991;329:977-986.

32. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(3):837-845.

33. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med 2016;15 (2):155-163.

34. Garofalo E, Bruni A, Pelaia C, Landoni G, Zangrillo A, Antonelli M, et al. Comparisons of two diaphragm ultrasound-teaching programs: a multicenter randomized controlled educational study. Ultrasound J 2019;11(1)–:6.

35. Matamis D, Soilemezi E, Tsagourias M, Akoumianaki E, Dimassi S, Boroli F, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. Intensive Care Med 2013;39(5):801-810.

36. Cammarota G, Sguazzotti I, Zanoni M, Messina A, Colombo D, Vignazia GL, et al. Diaphragmatic ultrasound assessment in subjects with acute hypercapnic respiratory failure admitted to the emergency department. Respir Care 2019;64(12):1469-1477.

37. Dubé BP, Dres M, Mayaux J, Demiri S, Similowski T, Demoule A. Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications. Thorax 2017;72(9):811-818.

38. Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. Crit Care 2015;19(1):161.

39. López-Barneo J, González-Rodríguez P, Gao L, Fernández-Agüera MC, Pardal R, Ortega-Sáenz P. Oxygen sensing by the carotid body: mechanisms and role in adaptation to hypoxia. Am J Physiol Cell Physiol 2016;310(8):C629-C642.

40. Easton PA, Slykerman LJ, Anthonisen NR. Ventilatory response to sustained hypoxia in normal adults. J Appl Physiol (1985) 1988;64 (2):521-528.

41. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. Am J Respir Crit Care Med 2018;197 (2):204-213.

42. Goligher EC, Brochard LJ, Reid WD, Fan E, Saarela O, Slutsky AS, et al. Diaphragmatic myotrauma: a mediator of prolonged ventilation and poor patient outcomes in acute respiratory failure. Lancet Respir Med 2019;7(1):90-98.

43. Goligher EC, Dres M, Patel BK, Sahetya SK, Beitler JR, Telias I, et al. Lung- and diaphragm-protective ventilation. Am J Respir Crit Care Med 2020;202(7):950-961.

44. Sassoon CSH, Zhu E, Caiozzo VJ. Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 2004;170(6):626-632.

45. Lee KH, Hui KP, Chan TB, Tan WC, Lim TK. Rapid shallow breathing (frequency-tidal volume ratio) did not predict extubation outcome. Chest 1994;105(2):540-543.

46. Tuinman PR, Jonkman AH, Dres M, Shi ZH, Goligher EC, Goffi A, et al. Respiratory muscle ultrasonography: methodology, basic and advanced principles and clinical applications in ICU and ED patients — a narrative review. Intensive Care Med 2020;46(4):594-605.

47. Longhini F, Maugeri J, Andreoni C, Ronco C, Bruni A, Garofalo E, et al. Electrical impedance tomography during spontaneous breathing trials and after extubation in critically ill patients at high risk for extubation failure: a multicenter observational study. Ann Intensive Care 2019;9(1):88.

48. Béduneau G, Pham T, Schortgen F, Piquilloud L, Zogheib E, Jonas M, et al. Epidemiology of weaning outcome according to a new definition the WIND study. Am J Respir Crit Care Med 2017;195:772-783.