Usefulness of Parasternal Intercostal Muscle Ultrasound during Weaning from Mechanical Ventilation

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Clinical trial number: not applicable

Prior presentations: American Thoracic Society 2018 (May 18-23, 2018, San Diego)

Acknowledgments: Not applicable

Word counts in the Abstract: 301

Word counts in the Introduction section: 270

Word counts in the Discussion section: 1411

Number of Figures: 4

Number of Tables: 5

Number of Appendices: not applicable

Number of Supplementary Digital Files :1

Abbreviated Title (Running Head): Intercostal muscle ultrasound and weaning

Summary Statement: Ultrasound of the parasternal intercostal muscle provides a direct evaluation of the respiratory load/capacity balance of the mechanically ventilated patients at the bedside. It may help to optimize the ventilator settings and to detect the readiness to be weaned of the critically ill patients.

Funding Statement
MD was supported by The French Intensive Care Society (SRLF bourse de mobilité 2015); The 2015 Short Term Fellowship program of the European Respiratory Society; The 2015 Bernhard Dräger Award for advanced treatment of ARF of the European Society of Intensive Care Medicine; The Assistance Publique Hôpitaux de Paris; The Fondation pour la Recherche Médicale (FDM 20150734498) and by Mitacs Globalink Sorbonne Universités. BPD was supported by a research grant from the Réseau en Santé Respiratoire du Québec and by fellowship grant from the Centre Hospitalier de l'Université de Montréal.

Conflict of interest Statements

AD reports personal fees and non-financial support from Medtronic, grants, personal fees and non-financial support from Philips, personal fees from Baxter, personal fees from Hamilton, grants and non-financial support from Fisher & Paykel, grants from French Ministry of Health. MD received personal fees from Lungpacer Inc. BPD received personal fees from Grifols, Boehringer Ingelheim and Roche, and has signed clinical research contracts with Sanofi, Roche and Boehringer Ingelheim. Thomas Similowski has received personal fees from Lungpacer Inc. and is a member of the board of a research association that has received, over the past ten years, unrestricted research grants from Maquet, Hamilton, Covidien, and Philips; he is the head of a research unit (UMRS 1158) that has signed research contracts with Air Liquide Medical Systems, France; he is listed as inventor or co-inventor on several patents, granted or pending, describing a brain-ventilator interface. LB's Research Laboratory received research grants from Covidien, General Electric, Fisher Paykel, Maquet (with St Michael's Hospital) and Philips. The others authors have no conflict of interest to disclose.

Abstract

Background

The assessment of diaphragm function with diaphragm ultrasound seems to bring important clinical information to describe diaphragm work and weakness. When the diaphragm is weak, extra-diaphragmatic muscles may play an important role but whether ultrasound can also assess their activity and function is unknown. This study aimed 1) to evaluate the feasibility of measuring the thickening of the parasternal intercostal and investigate the responsiveness of this muscle to assisted ventilation, and 2) to evaluate whether a combined evaluation of the parasternal and the diaphragm could predict failure of a spontaneous breathing trial.

Methods

First, an exploratory evaluation of the parasternal in 23 healthy subjects. Second, the responsiveness of parasternal to several pressure support levels were studied in 16 patients. Last, parasternal activity was compared in presence or absence of diaphragm dysfunction (assessed by magnetic stimulation of the phrenic nerves and ultrasound) and in case of success/failure of a spontaneous breathing trial in 54 patients.

Results

The parasternal was easily accessible in all patients. The inter-observer reproducibility was good (intra-class correlation coefficient 0.77 (95% confidence interval: 0.53 to 0.89). There was a progressive decrease in parasternal muscle thickening fraction with increasing levels of pressure

support (Spearman rho=-0.61 (95% confidence interval: -0.74 to -0.44), p<0.0001) and an inverse correlation between parasternal muscle thickening fraction and the pressure generating capacity of the diaphragm (Spearman rho=-0.79 (95% confidence interval: -0.87 to -0.66), p<0.0001). The parasternal muscle thickening fraction was higher in patients with diaphragm dysfunction: 17% (10 to 25) vs 5% (3 to 8), p<0.0001. The pressure generating capacity of the diaphragm, the diaphragm thickening fraction and the parasternal thickening fraction similarly predicted failure or the spontaneous breathing trial.

Conclusions

Ultrasound assessment of the parasternal intercostal muscle is feasible in the intensive care unit and provides novel information regarding the respiratory capacity load balance.

Keywords: Ultrasound, respiratory muscles, parasternal muscle, diaphragm, mechanical ventilation

Introduction

Critically ill patients frequently develop respiratory muscle dysfunction that may contribute to difficult and prolonged weaning from mechanical ventilation. Monitoring of the respiratory muscles function is therefore very useful during the weaning process.[1] Through several approaches that include the assessment of respiratory muscles pressure generating capacity[2] or the use of electromyogram[3], the evaluation of the respiratory capacity/load balance is possible at the bedside.[1,4] To this end, there has been a growing interest in diaphragm ultrasound as it provides a direct visualization of the muscle and its functioning.[5,6] However, parasternal intercostal and neck muscles also contribute to the generation of tidal volume.[7] Their contribution is known to increase in case of diaphragm dysfunction or increased respiratory load.[8,9] As these situations are frequently encountered in the intensive care unit, parasternal intercostal muscle ultrasound could provide additional information in the assessment of the respiratory capacity/load balance. A study reported the feasibility and validity of parasternal intercostal muscle ultrasound in patients with stable chronic obstructive pulmonary disease (COPD).[10] This original approach echoes electromyographic findings where neural drive – as measured through surface electromyogram of the second intercostal space parasternal muscle – has been proven to predict the risk of clinical deterioration in chronic obstructive pulmonary disease inpatients.[11] Since limited research has focused on the use of parasternal intercostal muscle ultrasound, the present work aimed at evaluating the feasibility and

reproducibility of measuring the parasternal intercostal muscle thickening (TFic) and at investigating the responsiveness of TFic to respiratory unloading during assisted ventilation. Secondary objectives were to investigate the relationship between TFic and diaphragm function and to evaluate whether measuring TFic could be helpful during the weaning process.

Methods

The main study was divided into three sub-studies, all were conducted between January 2015 and December 2016 in two sites: at the outpatient clinic at the Toronto Western Hospital, Toronto, Canada and at the Respiratory and Medical Critical Care Department, Hôpital Pitié-Salpêtrière, Paris, France (Figure 1 which displays characteristics of each sub-study). Across three studies, parasternal intercostal ultrasound was performed in different conditions. All subjects, or their next of kin in the case of the critically ill patients, provided written informed consent. The study was approved by the Institutional Review Boards at both participating institutions (CPP6/84-14 – 2014-A01168-39, CPP6/52-14 – 2014-A00715-42 and Toronto University Health Network: 15-8998) and has been performed in accordance with the ethical standards laid down in the 2008 Declaration of Helsinki.

Measurements

Parasternal intercostal muscle ultrasound. The full detailed method for right parasternal intercostal ultrasound is reported in the Supplemental Digital Content. A 10-15 MHz linear array transducer was positioned perpendicular to the anterior thorax surface in the longitudinal scan, at the level of the second right intercostal space, approximately 6-8 cm lateral to the sternal edge with a window visualising the 2nd and 3rd ribs. The second right parasternal intercostal muscle was identified as a three-layered biconcave structure: two linear hyperechoic membranes respectively running from the anterior and posterior aspects of the adjoining ribs, and a medial portion with muscle echotexture (see Figure 2 and Video E1 in the Supplemental Digital Content which is a cine-loop of the parasternal intercostal ultrasound). Using M-mode,

the ultrasound beam was perpendicularly directed at the midsection of the muscle, where it is the thinnest at end-expiration. The thickness of the parasternal intercostal muscle was measured on frozen images at end-expiration and at peak inspiration. Change in thickness determined the thickening fraction of the parasternal intercostal muscle (TFic) as follows: TFic equals peak inspiration thickness minus end expiratory thickness divided by end expiratory thickness. All measurements were repeated on at least three separate breaths and their average was reported. For the sake of feasibility and convenience, ultrasound was performed on the right parasternal intercostal muscle only.

Diaphragm ultrasound. Diaphragm ultrasound was conducted using a 4-12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, MA, USA). Diaphragm thickness was measured at end-expiration and at peak inspiration and thickening fraction (TFdi) was calculated offline as follows: TFdi equals peak inspiration thickness minus end expiratory thickness divided by end expiratory thickness. The full detailed method for diaphragm ultrasound has been reported elsewhere.[12]

Phrenic nerve stimulation. Diaphragm pressure generating capacity was assessed in terms of changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion (Ptr,stim) in sub-study C. Phrenic nerve stimulation was performed by bilateral anterior magnetic stimulation as reported elsewhere[4,13] (see the Supplemental Digital Content that displays a detailed description of the technique).

Subjects and studies design

The study was made of three sub-studies named A, B and C.

Study A was a physiological study dedicated to evaluate the reproducibility and values of parasternal intercostal muscle thickness and TFic in healthy subjects. Healthy subjects were adults naive from smoking exposure and without prior history of cardiopulmonary or neuromuscular disease who were enrolled prospectively during a six-month period. Parasternal intercostal muscle ultrasound was performed while subjects were breathing quietly, after a 30-minutes rest period. In random order, two observers, both experienced in respiratory muscles ultrasound, measured peak inspiratory and end expiratory thickness. Observers were blinded to each other's findings. Each observer performed two series of measurements separated by 20 minutes to allow intra-observer reproducibility calculation.

Study B was a physiological study conducted in mechanically ventilated patients within the Respiratory and Critical Care Department, Hôpital Pitié Salpêtrière, Paris. It aimed at assessing TFic and TFdi at pressure support levels varying from the lowest to the highest to better describe the dose response relationship. Patients were enrolled prospectively over a four-month period. They were eligible if they had been invasively mechanically ventilated for >24 hours through tracheal intubation and were currently ventilated in pressure support mode. The decision to initiate pressure-support ventilation was taken by the attending physician who was not involved in the study (see *Supplemental Material*) for the criteria used to initiate pressure support mode). Parasternal intercostal muscle ultrasound was performed at the following pressure support levels applied in a random sequence order: 5, 10, 15 and 20 cmH_2O while positive end-expiratory pressure (PEEP) was set to 5 cm H_2O. In addition, a last

condition was studied with a pressure support of 7 cmH_2O and PEEP set to 0 cm H_2O. Inspired fraction of O_2 was set to 30% in all cases and was not changed during the study. Investigators conducting ultrasound measurements were blinded to ventilator settings. Each condition was maintained for ten minutes and ultrasound measurements were performed during the last two minutes. Ultrasound measurements were performed by a physician with experience in respiratory muscle ultrasound. A five-minute resting period during which the initial ventilator settings were reapplied was allowed between conditions.

Study C was part of a clinical study conducted in mechanically ventilated patients within the Respiratory and Critical Care Department, Hôpital Pitié Salpêtrière, Paris.[12] Some data from this cohort have been published elsewhere.[12-14] This primary study aimed to determine the prevalence and impact of diaphragm dysfunction at the time of weaning and to evaluate the potential interest of respiratory muscles ultrasound in mechanically ventilated patients. Study C aimed at investigating the relationship between TFic and diaphragm pressure-generating capacity as well as weaning outcome. Study C enrolled patients prospectively over an eight-months period. Patients were eligible if they had been mechanically ventilated through an endotracheal tube for >24 hours and were deemed ready to undergo a first spontaneous breathing trial as decided by their attending physician according to criteria derived from the International Conference on Weaning (see the Supplemental Digital Content for a full description of the weaning protocol).[15] Non-inclusion criteria for this study were mainly related to contraindication to magnetic stimulation of the phrenic nerves. Diaphragm function was assessed in term of change in Ptr,stim.[4] A

Ptr,stim <11 cmH_2O was used to define diaphragm dysfunction.[4,13] Following this, parasternal intercostal ultrasound and diaphragm ultrasound was performed while patients were ventilated under pressure support ventilation with PEEP of 5 cmH_2O and pressure support set to reach a tidal volume of 6-8 ml/kg of predicted ideal body weight. Then, a 30-minutes spontaneous breathing trial performed under a pressure support of 7 cmH_2O and PEEP set to zero was performed. The spontaneous breathing trial was defined as successful if patients had no sign of clinical intolerance during all the 30-minutes period. Otherwise, the spontaneous breathing trial was defined as a failure. In a subset of 15 patients from this sub-study, ultrasound measurement of end expiratory thickness and peak inspiratory thickness and TFic were assessed by two observers to assess inter-observer reliability.

Statistical analyses

Normality of the distribution of variables was assessed using the Kolmogorov-Smirnov test. Variables are presented as median (interquartile range) or number (%).

All three studies were conducted prospectively and index tests were planned before data collection. Two observers performed ultrasound to assess reproducibility of parasternal intercostal muscle measurements in healthy (study A) and in patients (study C). Reproducibility of diaphragm ultrasound has been reported elsewhere[16,17].

For Study A, intra- and inter-rater reliability was analysed using intra-class correlation coefficient for parasternal intercostal end expiratory thickness, peak inspiratory thickness and TFic. Parasternal intercostal end expiratory thickness, peak inspiratory thickness and TFic between females and males were compared by Mann-

Whitney test. As an exploratory study, sample size was estimated from previous publications[17–19] and a convenience sample of 23 subjects was deemed necessary.

For study B, Friedman test and Dunn's multiple comparisons was used to compare the different values of TFic and TFdi across conditions. Sample size was estimated from previous publications[17,20] and a convenience sample of 16 patients was deemed necessary.

For study C, the relationship between Ptr,stim and TFic was evaluated using Spearman correlation. Differences between patients with and without diaphragm dysfunction and between those with spontaneous breathing trial failure or success were assessed using Mann-Whitney test or chi-square tests, where appropriate. The manuscript conforms to the "Essential Items for Reporting Diagnostic Accuracy Studies" checklist for reporting of studies of diagnostic accuracy.[21] The relationship between TFic and TFdi was assessed by computing the ratio TFic/TFdi. Receiver Operating Characteristic curves were constructed to evaluate the performance of four indices to predict weaning failure: Ptr,stim, TFdi, TFic and TFic/TFdi ratio. Sensitivities, specificities, positive and negative predictive values, positive and negative likelihood ratios and areas under the Receiver Operating Characteristic curves were calculated. Areas under the receiver operating characteristic curves were performed to identify optimal cut-off values in predicting failure, and these estimates were obtained using bootstrapping with 1000 replications. The best threshold value for each index was determined as the value associated with the best Youden index for the prediction of failure. Areas under the receiver operating characteristic curves were compared using the non-parametric approach of DeLong et al.[22] Inter-observer

reliability of the parasternal intercostal muscle ultrasound measurements was assessed using intra-class coefficient correlation in a subset of 15 patients. In this cohort, inter-observer reliability of the diaphragm ultrasound measurements has already been reported elsewhere.[12] There was no missing data nor loss of follow-up. In all cases, a p-value <0.05 was considered statistically significant and two-tailed testing was used to test hypothesis. All analyses were performed using SPSS, v.21 (IBM, Chicago, Illinois, USA) and MedCalc Software (bvba, Ostend, Belgium).

Results

Sub-study A: healthy subjects

Twenty-three subjects were recruited. Values of parasternal intercostal end expiratory thickness and peak inspiratory thickness were higher in men than in women, but values of TFic were similar between genders (Table 1). Intra-Class coefficient correlation between observers for the measurements of parasternal intercostal end expiratory thickness and peak inspiratory thickness were 0.92 (CI 95%: 0.82 to 0.96) and 0.92 (CI 95% 0.82 to 0.96) respectfully and only 0.77 (CI 95% 0.53 to 0.89) for TFic, but TFic values were very low in these healthy subjects at rest (median 3%, CI 95%: 2 to 5) (Figure 3). Table E1, Supplemental Digital Content 1, displays the intra-class correlation coefficients of parasternal intercostal muscle ultrasound measurements.

Study B: Parasternal intercostal muscle responsiveness to ventilatory support

Sixteen patients participated in the study B (see Figure 1 that shows the flow chart of the study). Their main characteristics are described in Table 2. The highest TFic and TFdi were measured with Pressure Support level of 7 cmH_2O and PEEP 0 cmH_2O and the lowest TFic and TFdi were measured with Pressure Support level of 20 cmH_2O and PEEP 5 cmH_2O (Figure 2 and Figure E1 in Supplemental Digital Content 1 that displays the simultaneous changes in TFdi and TFic). There was a correlation between Pressure Support level and TFic (Spearman rho=-0.61 (CI 95%: -0.74 to -0.44), $p<0.0001$).

Study C: Parasternal intercostal muscle, diaphragm function and weaning outcome

Of the 294 patients admitted during the study period, 54 were enrolled in study C (see Figure 1 that shows the flow chart of the study). Patients characteristics are displayed in Table 2. Among them, 33 (61%) had diaphragm dysfunction and 21 (39%) did not. Pressure Support and PEEP level were similar in the two groups, but tidal volume was lower in patients with diaphragm dysfunction (Table 3). Table E1 in Supplemental Digital Content 1 displays the intra-class correlation coefficients of parasternal intercostal muscle ultrasound measurements.

Relationship between parasternal intercostal muscle and diaphragm function

Patients with diaphragm dysfunction had higher TFic compared to patients without diaphragm dysfunction (Table 3). There was a inverse curvilinear correlation between Ptr,stim and TFic (Spearman rho=-0.79 (CI 95%: -0.87 to -0.66), p<0.0001, see Figure 4). –

Relationship between parasternal intercostal muscle, diaphragm function and weaning outcome

Among the 54 included patients, 22 (41%) failed the spontaneous breathing trial (Table 4). Patients who failed spontaneous breathing trial had lower Ptr,stim value, lower TFdi, higher TFic and lower TFic/TFdi ratio (Table 4). Predictive performances and best cut-offs of the four indices to predict failure are displayed in Table 5. No difference was found between areas under the receiver operating characteristic curves of the four indices (See Table E2 in Supplemental Digital Content 1, that shows the comparison of areas under the receiver operating characteristic curves of the four indices to predict spontaneous breathing trial failure).

Discussion

The main findings are summarized as follows: 1) measurement of TFic was feasible and reproducible, 2) TFic was responsive to respiratory load, 3) a greater TFic under pressure support ventilation was associated with diaphragm dysfunction and failure of a spontaneous breathing trial and 4) TFic in combination with TFdi gave similar information than TFic alone.

Anatomy and physiology of intercostal muscles

The intercostal muscles form two thin layers that span each of the intercostal spaces. Ventrally, between the sternum and the chondrocostal junctions, the external intercostal muscles are replaced by a fibrous aponeurosis conventionally called the "parasternal intercostal muscles". In dogs, parasternal intercostal denervation significantly decreases the expansion of the rib cage during inspiration.[23] In humans, electrophysiological data suggest that parasternal intercostal muscles have an inspiratory mechanical advantage and that this advantage decreases gradually from the second to the fifth interspace.[24] The parasternal intercostal muscles are active only during the inspiratory phase of the breathing cycle and interact together with the diaphragm and other extra-diaphragmatic inspiratory muscles. By contrast to other extra-diaphragmatic inspiratory muscles such as scalens or sternocleidomastoids located in the neck, the ultrasound window of parasternal intercostal has the advantage to be usually free of health care equipment (tracheostomy, intravascular lines). This study endeavored to investigate with ultrasound the parasternal intercostal activity.

TFic as a bedside indicator of the respiratory load – capacity balance

Extra diaphragmatic inspiratory muscles are responsive to respiratory load.[25,26] In the ICU, extra diaphragmatic inspiratory muscle electromyogram activity is a surrogate of respiratory drive.[3] As a matter of fact, increased extra diaphragmatic inspiratory muscle electromyogram activity is associated with insufficient level of inspiratory pressure support during weaning from mechanical ventilation[27], weaning failure[8], and dyspnea.[3] In addition, the electromyographic activity of the parasternal intercostal muscle, is a marker of treatment response and predicts the outcome during acute exacerbation of COPD.[11,28] Our results confirm these data as we report a dose response relationship between parasternal intercostal muscle thickening fraction and respiratory load (study B). This relationship suggests that the parasternal intercostal muscle thickening fraction is a relevant tool to assess the load/capacity balance in critically ill patients. Our approach was to use ultrasound, a non-invasive tool, widely available and that provides a real time assessment of muscle contraction. Data on parasternal intercostal muscle ultrasound are scarce. In an animal model, ultrasound morphometric assessment of the intercostal parasternal muscle was similar to measurement performed directly on the specimen, demonstrating the ability of ultrasound to accurately estimate the anatomical structure of the parasternal intercostal muscle.[29] In addition, the good inter-observer repeatability of the ultrasound measurement of parasternal intercostal muscle thickness has also been reported in humans[10,29,30] and are in line with our own reproducibility findings. It suggests that ultrasound measurement of parasternal intercostal thickness and thickening fraction is feasible and reproducible, and that the technique can reliably be employed. Remarkably, the parasternal intercostal muscle thickness was higher for

the ICU patients than for the healthy subjects but similar to what has been reported in COPD patients.[10] While the exact reasons of this increase in thickness is unclear (edema, inflammation, injury), it may reflect an over-recruitment of the extradiaphragmatic muscles that occurs in the intensive care unit patients. Further studies will have to specifically focus on this point.

Relationship between TFic and diaphragm function

The relationship between diaphragm function and the recruitment of extra-diaphragmatic inspiratory muscles has been described in animal models and in humans, although few data are available in intensive care unit patients.[8,31–34] The diaphragm is the main inspiratory muscle and diaphragm dysfunction elicits a series of adaptive mechanisms that enable ventilation and pulmonary gas exchange to be maintained within reasonable limits. Patients with chronic diaphragm dysfunction exhibit an increase in extra-diaphragmatic inspiratory muscles contraction that is associated with respiratory discomfort.[35,36] Conversely, diaphragm paralysis results in a marked increase in parasternal intercostal muscle activity while minute ventilation is relatively unaffected.[31,37] In situation of high respiratory drive, diaphragm dysfunction is associated with a significant increase in the contractile activity of the extra-diaphragmatic respiratory muscles.[31,32] The extra diaphragmatic respiratory muscles recruitment is therefore a mechanism of compensation that can be activated in presence of diaphragm dysfunction. We evidenced this mechanism in our patients by showing a higher TFic in those who had a diaphragm dysfunction as compared to their counterparts. Difference between groups was very clear as the TFic value in patients with diaphragm dysfunction was on average three times higher than in patients

without diaphragm dysfunction. Moreover, we observed a negative curvilinear relationship between TFic and diaphragm function. It suggests an exponential increase in TFic under a critical value of Ptr,stim. In our patients, this value appeared lower than the Ptr,stim-threshold that classically defines diaphragm dysfunction. This finding suggests that the recruitment of parasternal intercostal muscle may start before diaphragm dysfunction – as it is classically defined[28,29] – is fully constituted. Subsequently, documenting such recruitment by ultrasound may encourage clinicians to raise the hypothesis of a diaphragm dysfunction. Alternatively, it may also indicate underassistance and may encourage caregivers to optimize the ventilator settings.

TFic, diaphragm thickening fraction and weaning outcome

Diaphragm function is an important determinant of spontaneous breathing trial outcome. However, investigating diaphragm function at bedside in the intensive care unit setting may be a challenge.[13,38] Diaphragm thickening fraction can be used as a surrogate of diaphragm function and is a reliable predictor of spontaneous breathing trial outcome.[5] However, a recent study highlighted that diaphragm ultrasound doesn't allow to predict extubation failure[39], justifying to explore extradiaphragmatic muscles. In the present study, we sought to examine whether either TFic or the addition of TFic to TFdi would improve the prediction of the trial outcome. Intercostal thickening fraction was higher in patients who failed the trial and appears to predict reasonably well the outcome of the spontaneous breathing trial, in the opposite fashion than TFdi (the higher the TFic, the worse the outcome). However, TFic did not perform better than TFdi, and neither did the combination of both indices. Nevertheless, we believe our findings are of importance since diaphragm ultrasound is

not always feasible and TFic could be an interesting alternative. Documenting an increased TFic before starting the spontaneous breathing trial could be relevant insofar it may encourage caregivers to search for a reason susceptible to destabilize the respiratory load/capacity balance.

As per our results in healthy breathing at rest, TFic is expected to be as low as possible. Otherwise, it may be the sign of extra-diaphragmatic respiratory muscles recruitment suggesting inappropriate patient's inspiratory effort. This may be potentially relevant in context of increasing awareness of the adverse effects of both strong and weak respiratory efforts during mechanical ventilation on patient outcome[40]. Since monitoring patient inspiratory effort is rarely done in routine because it requires invasive procedure (esophageal catheter), performing parasternal intercostal ultrasound could be an alternative approach to provide a qualitative estimate of high inspiratory effort.

Limits

Our study has limitations. First, all ultrasound procedures were performed on the right side only in the study. This approach was chosen to facilitate the acquisition of ultrasound images. In addition, we assumed TFic of the right parasternal intercostal muscle to be a surrogate of the overall parasternal intercostal function since we did not assess all parasternal intercostal muscles separately. This approach is however usually taken in such physiological studies, in particular when using electromyogram.[28] Second, TFic cut-off to predict spontaneous breathing trial outcome was determined while patients were receiving a standardized amount of ventilator support (i.e. pressure-support level targeting a tidal volume of 6-8 ml/kg of ideal body weight).

Therefore, this cut-off may be only valid in the ventilatory conditions under which measurements were performed. Such ventilatory settings, however, are in line with common practices and recommendations in the ICU setting and therefore are easily generalizable. Third, the causes of spontaneous breathing trial failure were not documented and it is likely that several reasons may explain the failure of the spontaneous breathing trial. However, the ultrasound measurements were made before conducting the spontaneous breathing trial while the patients were supposed to be adequately assisted. Therefore, the use of ultrasound to detect situations at high risk of spontaneous breathing trial failure remains clinically relevant whatever the causes of failure. Fourth, while the use of respiratory muscles ultrasound is growing in the intensive care unit, it remains challenging to generalize its use to non-expert operators. Currently, there is no standard definition of adequate training. As a monocentric and pilot study, our findings warrant further confirmation with a larger number of patients and non-expert ultrasound observers.

Conclusion

Parasternal intercostal muscle ultrasound appears feasible and potentially helpful in mechanically ventilated patients to estimate inadequate inspiratory efforts in case of unbalanced load/capacity respiratory capacity. In the context of increasing awareness of the risk of overestimation and underestimation of patient's inspiratory effort, parasternal intercostal muscle and diaphragm ultrasound may constitute a valuable alternative to the classical invasive monitoring tools.

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Figures legends

Figure 1. Characteristics and flow chart of each sub-study
SBT: spontaneous breathing trial, PS: pressure support

Figure 2. Ultrasound of the right parasternal intercostal muscle
Left panel: The parasternal intercostal muscle was identified as a three-layered biconcave structure: two linear hyperechoic membranes respectively running from the anterior and posterior aspects of the adjoining ribs, and a medial portion with muscle echotexture. Measurement in B-mode was taken at the central, thinnest section of the muscle (dotted line).
Right panel: Using M-mode, the thickness of the parasternal intercostal muscle was measured on frozen images at end-expiration (Tee) and end-inspiration (Tei).

Figure 3. Parasternal intercostal muscle thickening fraction (TFic) (median, interquartile) at various levels of pressure support (PS) and positive end-expiratory pressure (PEEP), zero end-expiratory pressure (ZEEP) and in the 23 healthy subjects breathing at rest (grey bar).
* $p<0.05$ as compared to PS 7 and ZEEP.

Figure 4. Relationship between parasternal intercostal muscle thickening fraction (TFic) and diaphragm pressure generating capacity as assessed with bilateral anterior magnetic stimulation of the phrenic nerves (Ptr,stim). The dotted line represents the Ptr,stim-cut-off of 11 cmH_2O under which diaphragm dysfunction is classically defined (2).

Usefulness of parasternal intercostal muscle ultrasound during weaning from mechanical ventilation

Supplemental Digital Content

METHODS

Study B

Decision to initiate pressure-support ventilation.

Study C

- Readiness criteria to undergo a first spontaneous breathing trial
- Contraindications to magnetic stimulation of the phrenic nerves
- Criteria defining failure of the spontaneous breathing trial
- Measurement: the phrenic nerve stimulation method

RESULTS

Table SDC1. Intra-class correlation – intra-observer variations of parasternal intercostal muscle ultrasound measurements in healthy subjects (study A) and patients (study C)

Table SDC2. Comparison of ROC curves of the four indices to predict spontaneous breathing trial failure

Figure SDC1. Changes in diaphragm thickening fraction (TFdi) and parasternal intercostal thickening fraction (TFic) under stepwise increase in pressure support (study B)

* as compared to pressure support (PS) 7 and positive end expiratory pressure zero (ZEEP) for TFdi

as compared to pressure support (PS) 7 and positive end expiratory pressure zero (ZEEP) for TFic

Figure SDC2. Receiver operating characteristics curves of endotracheal pressure induced by a bilateral phrenic nerve stimulation (**Ptr,stim**), diaphragm thickening fraction (**TFdi**), parasternal intercostal muscle thickening fraction (**TFic**) and **TFic/TFdi ratio** to predict failure of the spontaneous breathing trial.

METHODS

Study B

Decision to initiate pressure-support ventilation.

Patients were considered ready to be placed on pressure-support ventilation if they could sustain this mode for at least 1 hour with:[1]

1) pressure support ≤24 cmH_2O
2) positive end-expiratory pressure ≤12 cmH_2O
3) total level of inspiratory pressure <30 cmH_2O
4) respiratory rate ≤24/min
5) tidal volume ≥5 ml/kg ideal body weight, without signs of labored breathing, as defined by retractions or recessions - sucking in of the skin around the ribs and the top of the sternum, or prominent use of accessory respiratory muscles.

Study C

Readiness criteria to undergo a first spontaneous breathing trial

The criteria used to assess the readiness for weaning were derived from the International Conference on Weaning:[2]

1) adequate oxygenation (SpO2 >90% on a fraction of inspired oxygen ≤40% and positive end expiratory pressure ≤8 cmH_2O)
2) respiratory rate ≤35/min
3) a cooperative cognitive state
4) stable cardiovascular status (systolic arterial blood pressure of 90-160 mmHg without or minimal vasopressors and heart rate ≤140/min)

Contraindications to magnetic stimulation of the phrenic nerves

1) cardiac pacemaker or defibrillator
2) cervical implants
3) cervical spine injury
4) pregnancy

Non-inclusion criteria for study C

1) suspicion of underlying hemi-diaphragm paralysis (defined as an elevation of >2.5 cm of one hemi-diaphragm compared to the other on chest radiograph),
2) pre-existing neuromuscular disorders,
3) age <18 years and
5) decision to withhold life-sustaining treatment.

Criteria defining failure of the spontaneous breathing trial

The criteria of failure of the spontaneous breathing trial were derived from the International Conference on Weaning.[2] The spontaneous breathing trial was considered to be a failure if at least one the following criteria was present:

1) blood oxygen saturation (SpO_2) of < 90 % with a fraction of inspired oxygen (FiO_2) ≥ 50 %;
2) acute respiratory distress (RR ≥ 40/min, agitation, cyanosis);
3) systolic arterial blood pressure of ≥ 180 mmHg;

4) cardiac arrhythmias;
5) respiratory acidosis [pH<7.32 with an arterial carbon dioxide tension ($PaCO_2$) of ≥50 mmHg].

If none of these failure criteria was present, the spontaneous breathing trial was considered as successfully completed.

Measurements

Parasternal intercostal muscle ultrasound. Patients and subjects were studied in a semi-recumbent position. A 10-15 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, MA, USA for patients and HFL-38xe, FUJIFILM Sonosite, Bothell, WA, USA for healthy subjects) was positioned perpendicular to the anterior thorax surface in the sagittal plane, at the level of the second right intercostal space, approximately 6-8 cm lateral to the sternal edge with a window visualising the 2nd and 3rd ribs. This intercostal space was chosen as the inspiratory effect of the external parasternal intercostal muscle is maximal at this location, compared to more caudal interspaces.[3] The second right parasternal intercostal muscle was identified as a three-layered biconcave structure: two linear hyperechoic membranes respectively running from the anterior and posterior aspects of the adjoining ribs, and a medial portion with muscle echotexture (Figure 1). Considering that during inspiration the muscle fibers of the parasternal intercostal contract, displacing the rib cage cranially and anteriorly[3] and that their mass remains constant, an increase in thickness of the muscular structure can be visualized

using ultrasound. Using M-mode, the ultrasound beam was perpendicularly directed at the midsection of the muscle, where it is the thinnest at end-expiration. The thickness of the parasternal intercostal muscle was measured on frozen images at end-expiration (Tee) and at peak inspiration (Tei). TFic was defined as the percent change in muscle thickness between expiration and inspiration. This change in thickness determined the thickening fraction of the parasternal intercostal muscle (TFic = (Tei - Tee)/Tee). All measurements were repeated on at least three separate breaths and their average was reported. For the sack of feasibility, ultrasound was performed on the right parasternal intercostal muscle only. Ultrasound measurements were performed by MD, BPD and SV.

Phrenic nerve stimulation method

Diaphragm pressure generating capacity was assessed in terms of changes in endotracheal tube pressure induced by bilateral phrenic nerve stimulation during airway occlusion (Ptr,stim). Phrenic nerve stimulation was performed by bilateral anterior magnetic stimulation. In brief, two figure-of-eight coils connected to a pair of Magstim® 200 stimulators (The Magstim Company, Dyfed, UK) were positioned immediately posterior to the sternomastoid muscles at the level of the cricoid cartilage. Stimulations were delivered at the maximum output intensity of the stimulator (100%) that is known to consistently result in supramaximal phrenic contraction.[4-7] Patients were studied in a standardized semi-recumbent position, as follows: end-expiratory pressure was set to zero and the patient was allowed to exhale during an end-

expiratory pause. Intrinsic positive end expiratory pressure was found when at relaxed end-expiration, the endotracheal pressure could not reach the zero baseline while the endotracheal tube was disconnected from the ventilator, manually occluded and by checking the absence of respiratory effort. While the endotracheal tube was manually occluded, bilateral anterolateral magnetic stimulation was performed. The absence of active respiratory efforts in response to stimulation was determined by checking the stability of the airway pressure signal. Two operators were required to achieve both stimulation and measurements. After determining the optimal position of the coils, at least three stimulations were performed at 100% of maximal output allowed by the stimulator. Stimulations were separated by at least 60-sec to avoid superposition. The average of the three measures was taken into account for analysis. Ptr,stim was defined as the amplitude of the negative pressure wave following stimulation, taken from baseline to peak. It was measured at the proximal external end of the endotracheal tube, using a linear differential pressure transducer (MP45 ±100 cmH2O, Validyne, Northridge, Calif., USA). The pressure signal was sampled and digitized at 128 Hz (MP30, Biopac Systems, Santa Barbara, Calif., USA or Powerlab, AD Instruments, Bella Vista, Australia) for subsequent data analysis.

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Tables

Table E1. Intra-class correlation – intra-observer variations of parasternal intercostal muscle ultrasound measurements in healthy subjects (study A) and patients (study C)

		Intra-Observer #1		Intra-Observer #2		Inter-Observer	
		ICC	95% CI	ICC	95% CI	ICC	95% CI
Study A	Tee	0.97	0.94 to 0.99	0.97	0.94 to 0.99	0.92	0.82 to 0.96
	Tei	0.97	0.94 to 0.99	0.97	0.92 to 0.99	0.92	0.82 to 0.96
	TFic	0.86	0.68 to 0.94	0.52	0.12 to 0.77	0.77	0.53 to 0.89
Study C	Tee	0.79	0.48 to 0.92	0.97	0.92 to 0.99	0.84	0.60 to 0.94
	Tei	0.91	0.77 to 0.97	0.97	0.93 to 0.99	0.95	0.88 to 0.98
	TFic	0.92	0.78 to 0.97	0.92	0.77 to 0.97	0.92	0.78 to 0.97

Tee: parasternal intercostal end-expiratory thickness; Tei: parasternal intercostal end-inspiratory thickness; TFic: parasternal intercostal muscle thickening fraction; ICC: intra-class correlation coefficient; CI: confidence interval

Table E2. Comparison of ROC curves of the four indices to predict spontaneous breathing trial failure

	Comparison with			

Variable	AUC	95% CI	Ptr,stim	TFdi	TFic	TFic/TFdi
Ptr,stim	0.91	0.80 to 0.97	-	p = 0.472	p = 0.415	p = 0.851
TFdi	0.88	0.76 to 0.97	-	-	p = 0.932	p = 0.402
TFic	0.89	0.76 to 0.95	-	-	-	p = 0.130
TFic/TFdi	0.92	0.81 to 0.96	-	-	-	-

Ptr,stim: endotracheal pressure induced by a bilateral phrenic nerve stimulation, TFdi: diaphragm thickening fraction; TFic: parasternal intercostal muscle thickening fraction; AUC: area under the receiver operating characteristics curves; CI: confidence interval

Figures

Figure E1

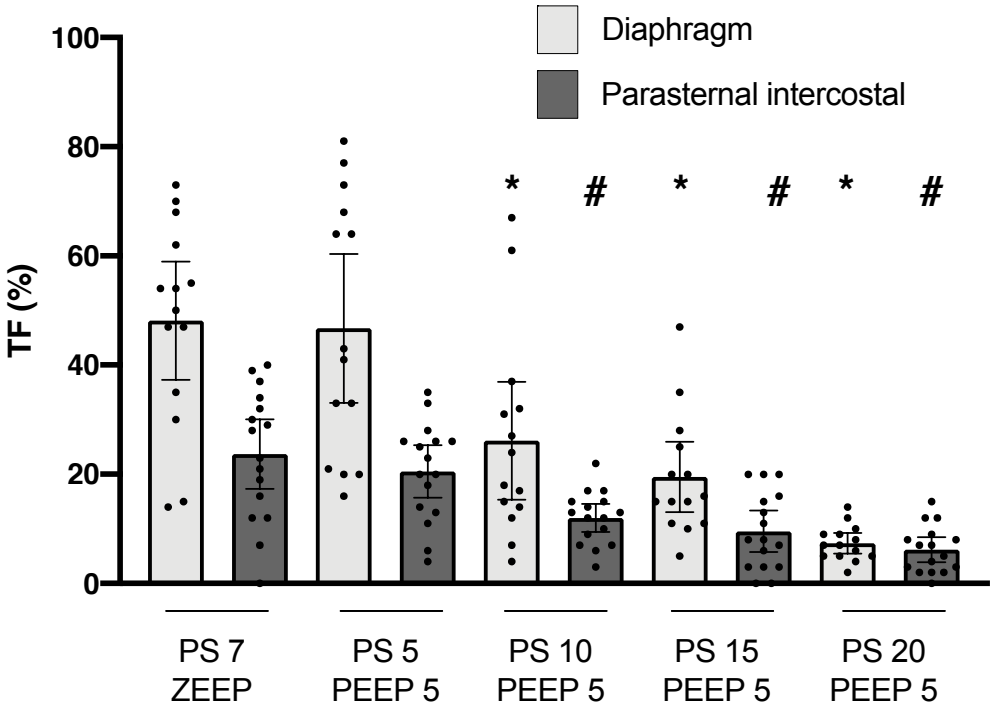

Figure E2

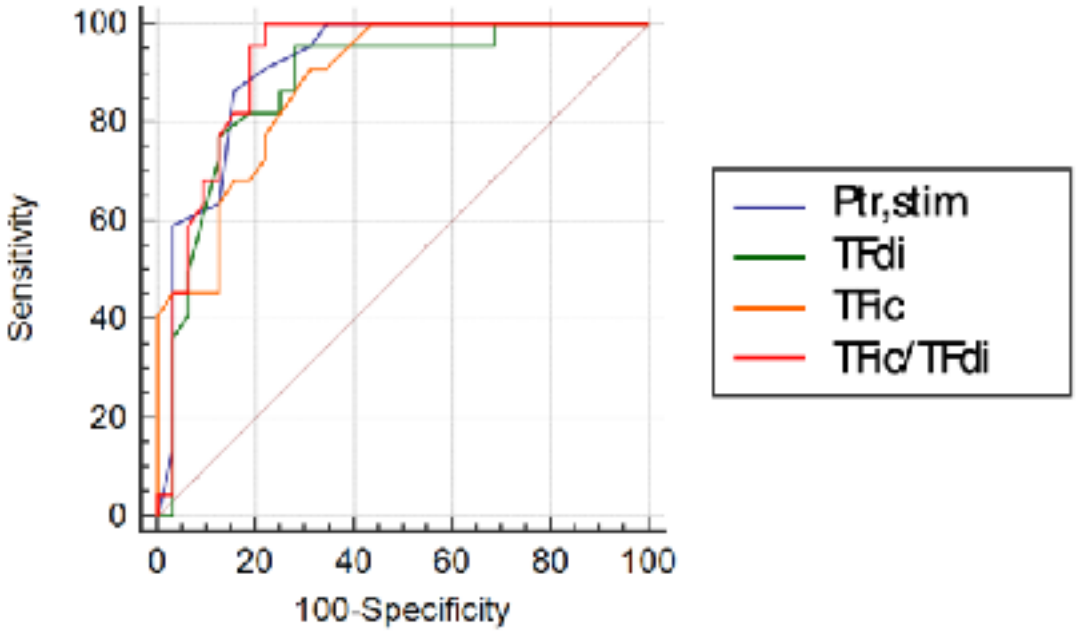

Table 1. Characteristics and parasternal intercostal muscle measurements in healthy subjects (study A)

	All	Male	Female	p
Characteristics, *n*	23	11	12	
Age, *years*	27 (25 to 36)	34 (26 to 36)	26 (24 to 29)	0.956
Weight, *kg*	67 (59 to 75)	75 (72 to 82)	60 (57 to 65)	<0.0001
Height, *cm*	1.70 (1.62 to 1.81)	1.81 (1.70 to 1.85)	1.63 (1.60 to 1.71)	0.001
Body Mass index, *kg/m²*	23 (21 to 25)	24 (23 to 26)	22 (20 to 24)	0.087
Intercostal muscle ultrasound				
End-inspiratory thickness, *mm*	2.8 (2.2 to 3.4)	3.3 (2.6 to 3.8)	2.2 (2.0 to 2.8)	<0.0001
End-expiratory thickness, *mm*	2.8 (2.1 to 3.3)	3.3 (2.8 to 3.9)	2.1 (1.9 to 2.8)	<0.0001
Thickening fraction, *%*	3 (2 to 5)	3 (2 to 5)	3 (0 to 5)	0.732

Comparisons were made between Males and Females (Mann-Whitney test).

Table 2. Baseline characteristics of ICU patients enrolled in sub-studies B and C

	Study B (n=16)	Study C (n=54)
Male, *n (%)*	8 (50)	39 (72)
Age, *years*	64 (59 to 78)	58 (48 to 67)
SOFA	8 (5 to 12)	
BMI, kg/m^2	23 (21 to 27)	24 (22 to 28)
Length of stay at inclusion, *days*	3 (2 to 6)	4 (2 to 6)
Length of MV at inclusion, *days*	3 (2 to 6)	4 (2 to 5)
Comorbidities, n (%)		
Cirrhosis	5 (31)	12 (22)
COPD	3 (19)	13 (24)
Central neurological disorders	5 (31)	14 (26)
Reason for ICU admission, n (%)		
Respiratory failure	7 (44)	20 (37)
Shock	4 (25)	20 (37)
Coma	5 (31)	14 (26)
Physiologic variables at inclusion		
Heart rate, min^{-1}	87 (76 to 98)	90 (78 to 104)
Mean arterial pressure, *mmHg*	85 (70 to 102)	79 (68 to 97)
Respiratory rate, min^{-1}	24 (17 to 26)	21 (19 to 25)
Arterial blood gases at inclusion		
pH	7.45 (7.41 to 7.48)	7.43 (7.37 to 7.45)
$PaCO_2$, *mmHg*	37 (33 to 41)	38 (38 to 46)
PaO_2/FiO_2 ratio	280 (227 to 325)	260 (205 to 332)

Data presented as n (%) or median (interquartile range).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation; ICU, intensive care unit; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; FiO_2, inspired fraction of oxygen.

Table 3. Characteristics of patients (study C) according to the presence of diaphragm dysfunction

	Diaphragm dysfunction (n=33)	No diaphragm dysfunction (n=21)	p
Sex, *males n (%)*	24 (73)	15 (71)	0.999
Age, *years*	61 (52 to 69)	56 (44 to 64)	0.111
BMI, *kg/m²*	24 (21 to 27)	25 (24 to 28)	0.457
Length of stay at inclusion, *days*	4 (2 to 7)	3 (2 to 6)	0.289
Length of MV at inclusion, *days*	4 (2 to 5)	3 (2 to 5)	0.510
SBT failure, *n (%)*	22 (67)	0 (0)	<0.0001
Ventilator settings			
Pressure support, *cmH_2O*	10 (8 to 10)	10 (8 to 10)	0.397
PEEP, *cmH_2O*	5 (5 to 5)	5 (5 to 5)	0.709
Tidal volume, *ml/kg PBW*	6.9 (5.8 to 7.8)	7.0 (5.9 to 8.3)	0.004
FiO_2, *%*	30 (30 to 40)	30 (30 to 30)	0.526
Respiratory rate, *min^{-1}*	22 (20 to 25)	21 (18 to 25)	0.746
Arterial blood gases at inclusion			
pH	7.41 (7.36 to 7.45)	7.44 (7.42 to 7.45)	0.182
$PaCO_2$, *mmHg*	41 (35 to 49)	37 (33 to 39)	0.079
PaO_2/FiO_2 ratio	257 (207 to 313)	266 (216 to 389)	0.325
Bicarbonates, *mmol/L*	25 (23 to 28)	25 (21 to 27)	0.684
Diaphragm function			
Ptr,stim, *cmH_2O*	6.0 (4.0 to 7.5)	14.0 (12.2 to 17.2)	<0.0001
Parasternal Intercostal muscle ultrasound			

End-expiratory thickness, *mm*	3.9 (3.2 to 5.2)	4.0 (3.1 to 5.0)	0.758
End-inspiratory thickness, *mm*	4.8 (3.9 to 6.2)	4.2 (3.3 to 5.4)	0.430
Thickening fraction, *%*	17 (10 to 25)	5 (3 to 8)	<0.003
Diaphragm ultrasound			
End-expiratory thickness, *mm*	2.2 (1.9 to 2.4)	2.4 (2.1 to 2.7)	0.272
End-inspiratory thickness, *mm*	2.6 (2.4 to 2.9)	3.3 (2.9 to 3.7)	0.002
Thickening fraction, *%*	19 (16 to 23)	39 (34 to 44)	<0.0001
TFic/TFdi ratio	0.9 (0.4 to 1.5)	0.2 (0.1 to 0.2)	0.003

Data presented as n (%) or median (interquartile).
MV; mechanical ventilation; SBT; spontaneous breathing trial; PEEP, positive end-expiratory pressure; PBW, predicted body weight; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; FiO_2, inspired fraction of oxygen; Ptr,stim, airway opening pressure in response to bilateral phrenic nerve stimulation; TFdi, diaphragm thickening fraction, TFic, parasternal intercostal muscle thickening fraction

Table 4. Characteristics of patients (study C) according to the outcome of the spontaneous breathing trial

	SBT failure (n=22)	SBT success (n=32)	p
Sex, *males n (%)*	16 (73)	23 (72)	0.999
Age, *years*	62 (52 to 69)	57 (44 to 65)	0.260
BMI, kg/m^2	24 (22 to 28)	25 (22 to 27)	0.544
Length of stay at inclusion, *days*	5 (3 to 9)	3 (1 to 5)	0.017
Length of MV at inclusion, *days*	5 (3 to 7)	3 (1 to 5)	0.011
Main reason for intubation			
Acute respiratory failure, *n (%)*	9 (41)	10 (31)	0.566
Shock , *n (%)*	9 (41)	12 (38)	0.999
Coma, *n (%)*	3 (14)	10 (31)	0.199
Ventilator settings at inclusion			
Pressure support level, cmH_2O	10 (8 to 10)	10 (8 to 10)	0.452
PEEP, cmH_2O	5 (5 to 5)	5 (5 to 5)	0.558
Tidal volume, *ml/kg PBW*	6.7 (5.6 to 8.0)	7.1 (5.9 to 8.8)	0.109
Respiratory rate, min^{-1}	22 (20 to 26)	21 (19 to 25)	0.399
Arterial blood gases at inclusion			
pH	7.40 (7.36 to 7.45)	7.44 (7.41 to 7.45)	0.064
$PaCO_2$, *mmHg*	44 (36 to 50)	37 (33 to 40)	0.008
PaO_2/FiO_2 ratio	231 (200 to 295)	300 (236 to 393)	0.012
Bicarbonates, *mmol/L*	27 (24 to 30)	24 (21 to 26)	0.303
Diaphragm function			
Ptr,stim, cmH_2O	8.9 (5.7 to 13)	11.9 (8.9 to 11.5)	<0.0001
Parasternal Intercostal muscle ultrasound			

End-expiratory thickness, *mm*	3.9 (3.1 to 4.7)	3.9 (3.2 to 5.3)	0.658
End-inspiratory thickness, *mm*	4.8 (3.9 to 5.5)	4.1 (3.5 to 5.9)	0.373
Thickening fraction, *%*	18 (10 to 33)	7 (4 to 10)	<0.0001
Diaphragm ultrasound			
End-expiratory thickness, *mm*	2.3 (2.0 to 2.5)	2.3 (1.9 to 2.6)	0.939
End-inspiratory thickness, *mm*	2.6 (2.3 to 2.9)	3.0 (2.7 to 3.3)	0.117
Thickening fraction, *%*	17 (13 to 21)	34 (29 to 38)	<0.0001
TFic/TFdi ratio	1.3 (0.7 to 2.1)	0.2 (0.1 to 0.4)	<0.0001

Data presented as n (%) or median (interquartile).
BMI, body mass index; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; PBW, predicted body weight; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; FiO_2, inspired fraction of oxygen; Ptr,stim, negative endotracheal pressure in response to phrenic nerve stimulation; TFdi, diaphragm thickening fraction, TFic, parasternal intercostal muscle thickening fraction

Table 5. Threshold, area under the receiver operating characteristics curves (AUC-ROC), sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values of endotracheal pressure induced by a bilateral phrenic nerve stimulation (Ptr,stim), diaphragm thickening fraction (TFdi), parasternal intercostal muscle thickening fraction (TFic) and TFic/TFdi ratio to predict failure of the spontaneous breathing trial.

	Threshold	AUC-ROC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Likelihood ratios (95% CI)		Predictive Values (%) (95% CI)	
					Positive	Negative	Positive	Negative
Ptr,stim	7.5 cmH_2O	0.91 (0.80 to 0.97)	91 (71 to 99)	81 (64 to 93)	4.85 (2.30 to 10.10)	0.11 (0.03 to 0.40)	77 (62 to 87)	93 (77 to 98)
TFdi	28.7 %	0.88 (0.77 to 0.95)	95 (77 to 100)	72 (53 to 86)	3.39 (1.90 to 5.90)	0.06 (0.01 to 0.40)	70 (57 to 80)	96 (77 to 99)
TFic	9.5 %	0.88 (0.76 to 0.95)	91 (71 to 99)	72 (53 to 86)	3.23 (1.80 to 5.70)	0.13 (0.03 to 0.50)	69 (56 to 80)	92 (75 to 98)
TFic/TFdi	0.35	0.92 (0.81 to 0.98)	100 (85 to 100)	78 (60 to 91)	4.62 (2.40 to 8.80)	0.02 (0.01 to 0.20)	76 (62 to 86)	100 (100 to 100)

CI: Confidence interval.