ANESTHESIOLOGY

Usefulness of Parasternal Intercostal Muscle Ultrasound during Weaning from Mechanical Ventilation

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Ultrasound can be used to assess work (*i.e.*, function) and weakness of the diaphragm. This can be helpful in predicting difficulty in weaning patients from mechanical ventilation.
- Patients who have weakness of the diaphragm may compensate with parasternal muscle activity. However, the feasibility of measuring parasternal intercostal muscle thickening with ultrasound and the ability of these measures to be combined with ultrasound evaluation of the diaphragm in order to predict ability to wean from mechanical ventilation has not been well explored.

What This Article Tells Us That Is New

- Parasternal intercostal muscle thickness can be measured with ultrasound with good interobserver reproducibility.
- Parasternal intercostal muscle thickening was responsive to the level of ventilator assistance and significantly higher (*i.e.*, increased) in mechanically ventilated patients with diaphragm dysfunction.
- The pressure-generating capacity of the diaphragm, the diaphragm thickening fraction, and the parasternal intercostal muscle thickening fraction were all significantly associated with failure of a spontaneous breathing trial in mechanically ventilated patients.

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, extradiaphragmatic muscles may play an important role, but whether ultrasound can also assess their activity and function is unknown. This study aimed to (1) evaluate the feasibility of measuring the thickening of the parasternal intercostal and investigate the responsiveness of this muscle to assisted ventilation; and (2) 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 interobserver reproducibility was good (intraclass correlation coefficient, 0.77 (95% CI, 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% CI, −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% CI, −0.87 to −0.66]; $P < 0.0001$). The parasternal muscle thickening fraction was higher in patients with diaphragm dysfunction: 17% (10 to 25) *versus* 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.

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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

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

Materials and Methods

The main study was divided into three substudies, all conducted between January 2015 and December 2016 at two sites: the outpatient clinic at the Toronto Western Hospital (Toronto, Canada) and the Respiratory and Medical Critical Care Department at Hôpital Pitié-Salpêtrière (Paris, France; see fig. 1 which displays characteristics of each substudy). 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; Toronto University Health Network, 15-8998) and was performed in accordance with the ethical standards set forth 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 1 (http://links.lww.com/ALN/C264). A 10- to 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 to 8 cm lateral to the sternal edge with a window visualizing the second and third 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 (fig. 2; and video in the Supplemental Digital Content 2, which is a cineloop of the parasternal intercostal ultrasound http://links.lww.com/ALN/C265). 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 as follows: parasternal intercostal muscle thickening 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- to 12-MHz linear array transducer (Sparq ultrasound system; Philips Healthcare, USA). Diaphragm thickness was measured at end expiration and at peak inspiration, and thickening fraction was calculated offline as follows: diaphragm thickening fraction 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 in substudy C. Phrenic nerve stimulation was performed by bilateral anterior magnetic stimulation as reported elsewhere[4,13] (see the Supplemental Digital Content 1 that displays a detailed description of the technique, http://links.lww.com/ALN/C264).

Subjects and Studies Design

The study was made of three substudies named A, B, and C. Study A was a physiologic study dedicated to evaluate the reproducibility and values of parasternal intercostal muscle thickness and parasternal intercostal muscle thickening in healthy subjects. Healthy subjects were adults naive from smoking exposure and without previous history of cardiopulmonary or neuromuscular disease who were enrolled prospectively during a 6-month period. Parasternal intercostal muscle ultrasound was performed while subjects were breathing quietly, after a 30-min rest period. In random order, two observers, both experienced in respiratory muscles ultrasound, measured peak-inspiratory and

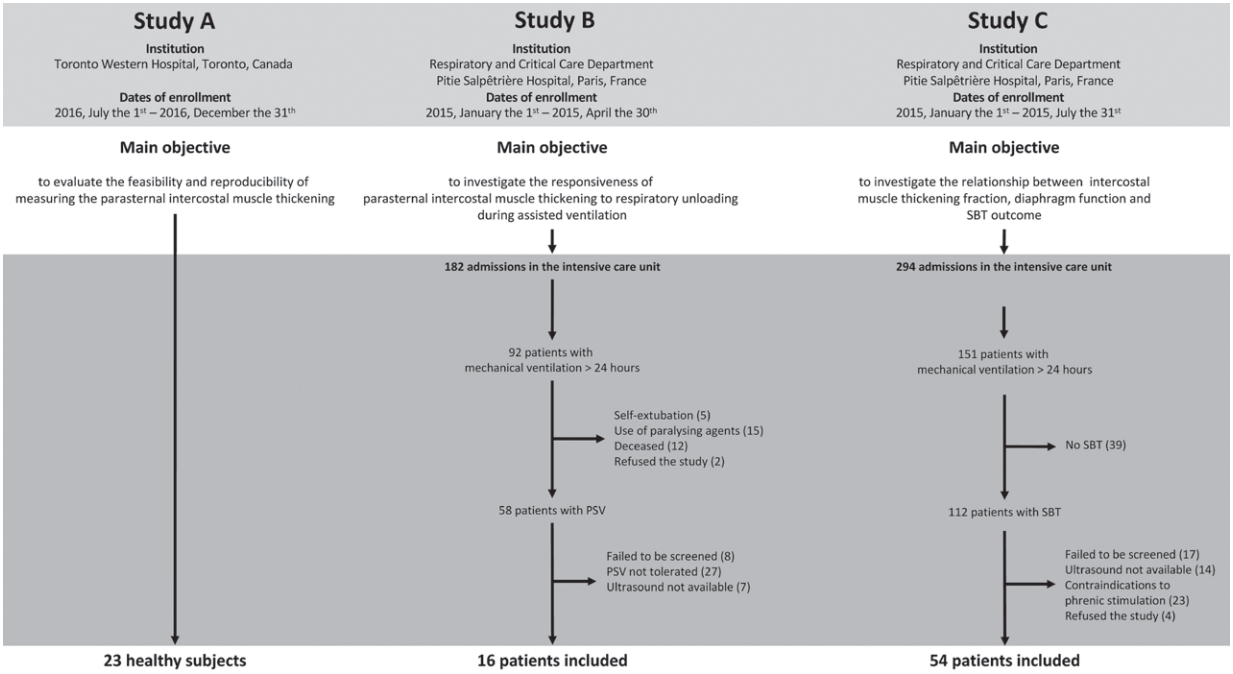

Fig. 1. Characteristics and flow chart of each sub-study. PSV, pressure support ventilation; SBT, spontaneous breathing trial.

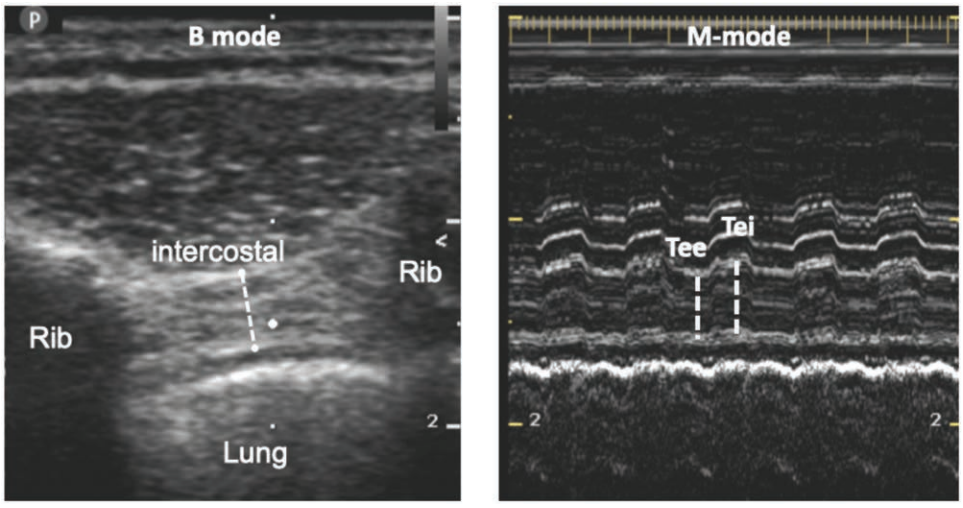

Fig. 2. Ultrasound of the right parasternal intercostal muscle. *(Left)* The parasternal intercostal muscle was identified as a three-layered biconcave structure: two linear hyperechoic membranes respectively running from the anterior and posterior aspects of the adjoining ribs, and a medial portion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

end-expiratory thickness. Observers were blinded to each other's findings. Each observer performed two series of measurements separated by 20 min to allow intraobserver reproducibility calculation.

Study B was a physiologic study conducted in mechanically ventilated patients within the Respiratory and Critical Care Department at Hôpital Pitié-Salpêtrière. It aimed at assessing parasternal intercostal muscle thickening and

diaphragm thickening fraction at pressure support levels varying from the lowest to the highest to better describe the dose–response relationship. Patients were enrolled prospectively during a 4-month period. They were eligible if they had been invasively mechanically ventilated for more than 24 h 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 Digital Content 1 for the criteria used to initiate pressure support mode, http://links.lww.com/ALN/C264). Parasternal intercostal muscle ultrasound was performed at the following pressure support levels applied in a random sequence order: 5, 10, 15, and 20 cm H_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 cm H_2O and PEEP set to 0 cm H_2O. Inspired fraction of oxygen 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 10 min and ultrasound measurements were performed during the last 2 min. Ultrasound measurements were performed by a physician with experience in respiratory muscle ultrasound. A 5-min 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 at Hôpital Pitié-Salpêtrière.[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 evaluate the potential interest of respiratory muscles ultrasound in mechanically ventilated patients. Study C aimed at investigating the relationship between parasternal intercostal muscle thickening and diaphragm pressure–generating capacity, as well as weaning outcome. Study C enrolled patients prospectively during an 8-month period. Patients were eligible if they had been mechanically ventilated through an endotracheal tube for more than 24 h 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 1 for a full description of the weaning protocol, http://links.lww.com/ALN/C264).[15] Noninclusion 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 bilateral phrenic nerve stimulation.[4] A bilateral phrenic nerve stimulation less than 11 cm H_2O was used to define diaphragm dysfunction.[4,13] After this, parasternal intercostal ultrasound and diaphragm ultrasound was performed while patients were ventilated under pressure support ventilation with PEEP of 5 cm H_2O and pressure support set to reach a tidal volume of 6 to 8 ml/kg of predicted ideal body weight. Then, a 30-min spontaneous breathing trial performed under a pressure support of 7 cm H_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-min period. Otherwise, the spontaneous breathing trial was defined as a failure. In a subset of 15 patients from this substudy, ultrasound measurement of end-expiratory thickness and peak-inspiratory thickness and parasternal intercostal muscle thickening were assessed by two observers to assess interobserver 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 interrater reliability was analyzed using intraclass correlation coefficient for parasternal intercostal end-expiratory thickness, peak-inspiratory thickness, and parasternal intercostal muscle thickening. Parasternal intercostal end-expiratory thickness, peak-inspiratory thickness, and parasternal intercostal muscle thickening 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 multiple comparisons were used to compare the different values of parasternal intercostal muscle thickening and diaphragm thickening fraction 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 airway opening pressure in response to bilateral phrenic nerve stimulation and parasternal intercostal muscle thickening 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 article conforms to the "Essential Items for Reporting Diagnostic Accuracy Studies" checklist for reporting of studies of diagnostic accuracy.[21] The relationship between parasternal intercostal muscle thickening and diaphragm thickening fraction was assessed by computing the ratio of parasternal intercostal muscle thickening to diaphragm thickening fraction. Receiver operating characteristic curves were constructed to evaluate the performance of four indices to predict weaning failure: airway opening pressure in response to bilateral phrenic nerve stimulation,

diaphragm thickening fraction, parasternal intercostal muscle thickening, and parasternal intercostal muscle thickening to diaphragm thickening fraction 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 1,000 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 nonparametric approach of DeLong *et al.*[22] Interobserver reliability of the parasternal intercostal muscle ultrasound measurements was assessed using intraclass coefficient correlation in a subset of 15 patients. In this cohort, interobserver 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 the hypothesis. All analyses were performed using SPSS, v.21 (IBM, USA) and MedCalc Software (bvba, Ostend, Belgium).

Results

Substudy 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 parasternal intercostal muscle thickening were similar between genders (table 1). Intraclass 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 parasternal intercostal muscle thickening, but parasternal intercostal muscle thickening values were very low in these healthy subjects at rest (median, 3%; CI 95%, 2 to 5; fig. 3). Table E1, Supplemental Digital Content 1 (http://links.lww.com/ALN/C264) 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 Study B (fig. 1 shows the flow chart of the study). Their main characteristics are described in table 2. The highest parasternal intercostal muscle thickening and diaphragm thickening fraction were measured with pressure support level of 7 cm H_2O and PEEP of 0 cm H_2O, and the lowest parasternal intercostal muscle thickening and diaphragm thickening fraction were measured with a pressure support level of 20 cm H_2O and PEEP of 5 cm H_2O (fig. 2; and fig. E1 in Supplemental Digital Content 1 displays the simultaneous changes in diaphragm thickening fraction and parasternal intercostal muscle thickening [http://links.lww.com/ALN/C264]). There was a correlation between pressure support level and parasternal intercostal muscle thickening (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 (fig. 1 shows the flow chart of the study). Patient 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 (http://links.lww.com/ALN/C264) displays the intraclass correlation coefficients of parasternal intercostal muscle ultrasound measurements.

Relationship between Parasternal Intercostal Muscle and Diaphragm Function. Patients with diaphragm dysfunction had higher parasternal intercostal muscle thickening

Table 1. Characteristics and Parasternal Intercostal Muscle Measurements in Healthy Subjects (Study A)

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

Comparisons were made between males and females (Mann–Whitney test).

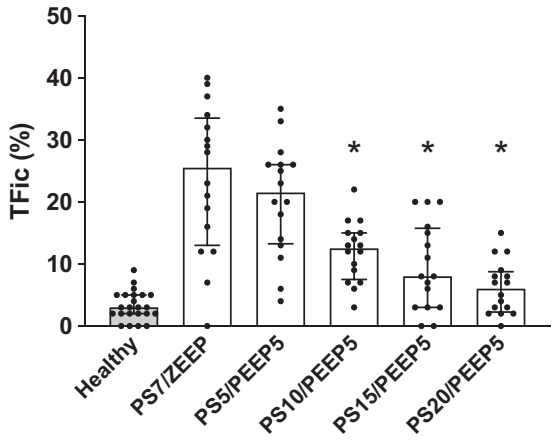

Fig. 3. Parasternal intercostal muscle thickening fraction (TFic) (median, interquartile) at various levels of pressure support ([PS] 5, 7, 10, 15, 20) and positive end-expiratory pressure (PEEP) and zero end-expiratory pressure (ZEEP), and in the 23 healthy subjects breathing at rest (*grey bar*). *$P < 0.05$ as compared to PS7 and ZEEP.

Table 2. Baseline Characteristics of ICU Patients Enrolled in Substudies B and C

	Study B (n = 16)	Study C (n = 54)
Male, n (%)	8 (50)	39 (72)
Age, yr	64 (59–78)	58 (48–67)
SOFA score	8 (5–12)	5 (4–8)
Body mass index, kg/m^2	23 (21–27)	24 (22–28)
Length of stay at inclusion, days	3 (2–6)	4 (2–6)
Length of MV at inclusion, days	3 (2–6)	4 (2–5)
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 (76–98)	90 (78–104)
Mean arterial pressure, mmHg	85 (70–102)	79 (68–97)
Respiratory rate, min^{-1}	24 (17–26)	21 (19–25)
Arterial blood gases at inclusion		
pH	7.45 (7.41–7.48)	7.43 (7.37–7.45)
$Paco_2$, mmHg	37 (33–41)	38 (38–46)
Pao_2/Fio_2 ratio	280 (227–325)	260 (205–332)

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

COPD, chronic obstructive pulmonary disease; Fio_2, inspired fraction of oxygen; ICU, intensive care unit; MV, mechanical ventilation; $Paco_2$, arterial partial pressure of carbon dioxide; Pao_2, arterial partial pressure of oxygen; SOFA, sequential organ failure assessment.

compared to patients without diaphragm dysfunction (table 3). There was a inverse curvilinear correlation between airway opening pressure in response to bilateral phrenic nerve stimulation and parasternal intercostal muscle thickening (Spearman $\rho = -0.79$ [CI 95%, −0.87 to −0.66]; $P < 0.0001$; fig. 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 airway opening pressure in response to bilateral phrenic nerve stimulation, lower diaphragm thickening fraction, higher parasternal intercostal muscle thickening and lower parasternal intercostal muscle to diaphragm thickening fraction 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 (table E2 in Supplemental Digital Content 1 shows the comparison of areas under the receiver operating characteristic curves of the four indices to predict spontaneous breathing trial failure [http://links.lww.com/ALN/C264]).

Discussion

The main findings are summarized as follows: (1) measurement of parasternal intercostal muscle thickening was feasible and reproducible; (2) parasternal intercostal muscle thickening was responsive to respiratory load; (3) a greater parasternal intercostal muscle thickening under pressure support ventilation was associated with diaphragm dysfunction and failure of a spontaneous breathing trial; and (4) parasternal intercostal muscle thickening in combination with diaphragm thickening fraction gave similar information than parasternal intercostal muscle thickening 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, electrophysiologic 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 extradiaphragmatic inspiratory muscles. By contrast to other extradiaphragmatic 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 healthcare equipment (tracheostomy,

Table 3. Characteristics of Patients (Study C) According to the Presence of Diaphragm Dysfunction

	Diaphragm Dysfunction (n=33)	No Diaphragm Dysfunction (n=21)	*P* Value
Sex, males n (%)	24 (73)	15 (71)	0.999
Age, yr	61 (52–69)	56 (44–64)	0.111
Body mass index, kg/m^2	24 (21 to 27)	25 (24–28)	0.457
Length of stay at inclusion, days	4 (2–7)	3 (2–6)	0.289
Length of MV at inclusion, days	4 (2–5)	3 (2–5)	0.510
SBT failure, n (%)	22 (67)	0 (0)	< 0.0001
Ventilator settings			
Pressure support, cm H_2O	10 (8–10)	10 (8–10)	0.397
PEEP, cm H_2O	5 (5–5)	5 (5–5)	0.709
Tidal volume, ml/kg PBW	6.9 (5.8–7.8)	7.0 (5.9–8.3)	0.004
FIO_2, %	30 (30–40)	30 (30–30)	0.526
Respiratory rate, min^{-1}	22 (20–25)	21 (18–25)	0.746
Arterial blood gases at inclusion			
pH	7.41 (7.36–7.45)	7.44 (7.42–7.45)	0.182
$PaCO_2$, mmHg	41 (35–49)	37 (33–39)	0.079
PaO_2/FIO_2 ratio	257 (207–313)	266 (216–389)	0.325
Bicarbonates, mmol/l	25 (23–28)	25 (21–27)	0.684
Diaphragm function			
Ptr,stim, cm H_2O	6.0 (4.0–7.5)	14.0 (12.2–17.2)	< 0.0001
Parasternal Intercostal muscle ultrasound			
End-expiratory thickness, mm	3.9 (3.2–5.2)	4.0 (3.1–5.0)	0.758
End-inspiratory thickness, mm	4.8 (3.9–6.2)	4.2 (3.3–5.4)	0.430
Thickening fraction, %	17 (10–25)	5 (3–8)	< 0.003
Diaphragm ultrasound			
End-expiratory thickness, mm	2.2 (1.9–2.4)	2.4 (2.1–2.7)	0.272
End-inspiratory thickness, mm	2.6 (2.4–2.9)	3.3 (2.9–3.7)	0.002
Thickening fraction, %	19 (16–23)	39 (34–44)	< 0.0001
Parasternal intercostal muscle thickening fraction/Diaphragm thickening fraction ratio	0.9 (0.4–1.5)	0.2 (0.1–0.2)	0.003

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

FIO_2, inspired fraction of oxygen; MV, mechanical ventilation; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Ptr,stim, airway opening pressure in response to bilateral phrenic nerve stimulation; SBT, spontaneous breathing trial.

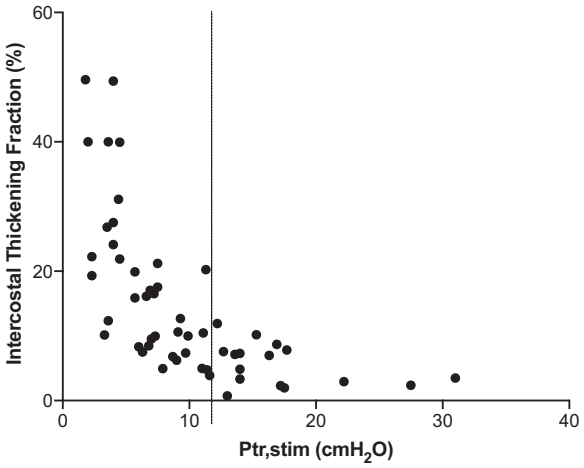

Fig. 4. Relationship between parasternal intercostal muscle thickening fraction and diaphragm pressure–generating capacity as assessed with airway opening pressure in response to bilateral phrenic nerve stimulation (Ptr,stim). The *dotted line* represents the Ptr,stim cut-off of 11 cm H_2O under which diaphragm dysfunction is classically defined (2).

intravascular lines). This study endeavored to investigate with ultrasound the parasternal intercostal activity.

Parasternal Intercostal Muscle Thickening as a Bedside Indicator of the Respiratory Load–Capacity Balance

Extradiaphragmatic inspiratory muscles are responsive to respiratory load.[25,26] In the intensive care unit, extradiaphragmatic inspiratory muscle electromyogram activity is a surrogate of respiratory drive.[3] As a matter of fact, increased extradiaphragmatic inspiratory muscle electromyogram activity is associated with an 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

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* Value
Sex, males n (%)	16 (73)	23 (72)	0.999
Age, yr	62 (52–69)	57 (44–65)	0.260
BMI, kg/m^2	24 (22–28)	25 (22–27)	0.544
Length of stay at inclusion, days	5 (3–9)	3 (1–5)	0.017
Length of MV at inclusion, days	5 (3–7)	3 (1–5)	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, cm H_2O	10 (8–10)	10 (8–10)	0.452
PEEP, cm H_2O	5 (5–5)	5 (5–5)	0.558
Tidal volume, ml/kg PBW	6.7 (5.6–8.0)	7.1 (5.9–8.8)	0.109
Respiratory rate, min^{-1}	22 (20–26)	21 (19–25)	0.399
Arterial blood gases at inclusion			
pH	7.40 (7.36–7.45)	7.44 (7.41–7.45)	0.064
P_{ACO_2}, mmHg	44 (36–50)	37 (33–40)	0.008
Pao_2/FIO_2 ratio	231 (200–295)	300 (236–393)	0.012
Bicarbonates, mmol/l	27 (24–30)	24 (21–26)	0.303
Diaphragm function			
Ptr,stim, cm H_2O	8.9 (5.7–13)	11.9 (8.9–11.5)	< 0.0001
Parasternal Intercostal muscle ultrasound			
End-expiratory thickness, mm	3.9 (3.1–4.7)	3.9 (3.2–5.3)	0.658
End-inspiratory thickness, mm	4.8 (3.9–5.5)	4.1 (3.5–5.9)	0.373
Thickening fraction, %	18 (10–33)	7 (4–10)	< 0.0001
Diaphragm ultrasound			
End-expiratory thickness, mm	2.3 (2.0–2.5)	2.3 (1.9–2.6)	0.939
End-inspiratory thickness, mm	2.6 (2.3–2.9)	3.0 (2.7–3.3)	0.117
Thickening fraction, %	17 (13–21)	34 (29–38)	< 0.0001
Parasternal intercostal muscle thickening fraction/Diaphragm thickening fraction ratio	1.3 (0.7–2.1)	0.2 (0.1–0.4)	< 0.0001

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

BMI, body mass index; FIO_2, inspired fraction of oxygen; MV, mechanical ventilation; P_{ACO_2}, arterial partial pressure of carbon dioxide; Pao_2, arterial partial pressure of oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Ptr,stim, airway opening pressure in response to bilateral phrenic nerve stimulation; SBT, spontaneous breathing trial.

Table 5. Threshold, AUC-ROC, Sensitivity, Specificity, Positive and Negative Likelihood Ratios, and Positive and Negative Predictive Values of Endotracheal Pressure Induced by a Ptr,stim, Diaphragm Thickening Fraction, Parasternal Intercostal Muscle Thickening Fraction, and Parasternal Intercostal Muscle Thickening Fraction/Diaphragm Thickening Fraction Ratio to Predict Failure of the Spontaneous Breathing Trial

					Likelihood Ratios (95% CI)		Predictive Values, % (95% CI)	
	Threshold	AUC-ROC (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive	Negative	Positive	Negative
Ptr,stim	7.5 cm H_2O	0.91 (0.80–0.97)	91 (71–99)	81 (64–93)	4.85 (2.30–10.10)	0.11 (0.03–0.40)	77 (62–87)	93 (77–98)
Diaphragm thickening fraction	28.7 %	0.88 (0.77–0.95)	95 (77–100)	72 (53–86)	3.39 (1.90–5.90)	0.06 (0.01–0.40)	70 (57–80)	96 (77–99)
Parasternal intercostal muscle thickening fraction	9.5 %	0.88 (0.76–0.95)	91 (71–99)	72 (53–86)	3.23 (1.80–5.70)	0.13 (0.03–0.50)	69 (56–80)	92 (75–98)
Parasternal intercostal muscle thickening fraction/Diaphragm thickening fraction	0.35	0.92 (0.81–0.98)	100 (85–100)	78 (60–91)	4.62 (2.40–8.80)	0.02 (0.01–0.20)	76 (62–86)	100 (100–100)

AUC-ROC, area under the receiver operating characteristics curves; CI, confidence interval; Ptr,stim, airway opening pressure in response to bilateral phrenic nerve stimulation.

ultrasound, a noninvasive tool that is widely available and 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 interobserver repeatability of the ultrasound measurement of parasternal intercostal muscle thickness has also been reported in humans,[10,29,30] and is 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 overrecruitment of the extradiaphragmatic muscles that occurs in the ICU patients. Further studies will have to specifically focus on this point.

Relationship between Parasternal Intercostal Muscle Thickening and Diaphragm Function

The relationship between diaphragm function and the recruitment of extradiaphragmatic inspiratory muscles has been described in animal models and in humans, although few data are available in ICU 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 extradiaphragmatic 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 extradiaphragmatic respiratory muscles.[31,32] The extradiaphragmatic 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 parasternal intercostal muscle thickening in those who had a diaphragm dysfunction as compared to their counterparts. Difference between groups was very clear as the parasternal intercostal muscle thickening 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 parasternal intercostal muscle thickening and diaphragm function. It suggests an exponential increase in parasternal intercostal muscle thickening under a critical value of bilateral phrenic nerve stimulation. In our patients, this value appeared lower than the bilateral phrenic nerve stimulation 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.

Parasternal Intercostal Muscle Thickening, 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 ICU 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 current study, we sought to examine whether either parasternal intercostal muscle thickening or the addition of parasternal intercostal muscle thickening to diaphragm thickening fraction 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 a fashion opposite to the diaphragm thickening fraction (the higher the parasternal intercostal muscle thickening, the worse the outcome). However, parasternal intercostal muscle thickening did not perform better than the diaphragm thickening fraction, nor did the combination of both indices. Nevertheless, we believe our findings are of importance since diaphragm ultrasound is not always feasible and parasternal intercostal muscle thickening could be an interesting alternative. Documenting an increased parasternal intercostal muscle thickening before starting the spontaneous breathing trial could be relevant insofar as it may encourage caregivers to search for a reason susceptible to destabilizing the respiratory load–capacity balance.

As per our results in healthy breathing at rest, parasternal intercostal muscle thickening is expected to be as low as possible. Otherwise, it may be a sign of extradiaphragmatic respiratory muscle recruitment suggesting a patient's inspiratory effort is inappropriate. This may be potentially relevant in the context of increasing awareness of the adverse effects of both strong and weak respiratory efforts during mechanical ventilation on patient outcomes.[40] Since monitoring patient inspiratory effort is rarely done in routine because it requires an 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 parasternal intercostal muscle thickening 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. However, this approach is usually taken in such physiologic studies, in particular when using electromyogram.[28] Second, the parasternal intercostal muscle thickening cut-off to predict a 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 to 8 ml/kg of ideal body weight). Therefore, this cut-off may only be 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 ICU, it remains challenging to generalize its use to nonexpert 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 nonexpert 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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Competing Interests

Dr. Demoule reports personal fees and nonfinancial support from Medtronic (Dublin, Ireland), grants, personal fees and nonfinancial support from Philips (Amsterdam, The Netherlands), personal fees from Baxter (Deerfield, Illinois), personal fees from Hamilton (Schaumburg, Illinois), grants and nonfinancial support from Fisher & Paykel (Aukland, New Zealand), grants from French Ministry of Health (Paris, France), personal fees from Getinge (Wayne, New Jersey), grants and personal fees from Respinor (Oslo, Norway), and grants and nonfinancial support from Lungpacer (Exton, Pennsylvania). Dr. Dres received personal fees from Lungpacer Inc. Dr. Dubé received personal fees from Grifols (Barcelona, Spain), Boehringer Ingelheim (Ingelheim am Rhein, Germany), and Roche (Basel, Switzerland), and has signed clinical research contracts with Sanofi (Paris, France), Roche, and Boehringer Ingelheim. Dr. 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 (Rastatt, Germany), Hamilton, Covidien (Dublin, Ireland), and Philips; he is the head of a research unit (UMRS 1158) that has signed research contracts with Air Liquide Medical Systems, (Antony, France); he is listed as inventor or coinventor on several patents, granted or pending, describing a brain–ventilator interface. Dr. Brochard's research laboratory received research grants from Covidien, General Electric (Boston, Massachusetts), Fisher & Paykel, Maquet (with St. Michael's Hospital), and Philips, and reports receiving equipment from Philips, Sentec (Fenton, Missouri), and Air Liquide. The other authors have no conflict of interest to disclose.

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