ANESTHESIOLOGY

Poor Correlation between Diaphragm Thickening Fraction and Transdiaphragmatic Pressure in Mechanically Ventilated Patients and Healthy Subjects

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Transdiaphragmatic pressure is proportional to the tension developed in the muscle fibers of the diaphragm.
- In research studies, transdiaphragmatic pressure can be estimated as a surrogate of diaphragm function using invasive catheters to record gastric and esophageal pressure. A derivative (pressure-time index) can be calculated from real-time analysis of pressure tracings.
- Interrogation of the diaphragm by ultrasound has recently become popular. The change in diaphragm thickness during inspiration (thickening fraction) has been proposed as an alternative approach to measure diaphragm function, although previous studies have reported wide variability in relationship to transdiaphragmatic pressure.

What This Article Tells Us That Is New

- Diaphragm thickening fraction and transdiaphragmatic pressure were compared using ultrasound and catheter pressure measurements from two previously published studies of 14 healthy and 25 mechanically ventilated patients.
- In healthy patients, moderate correlations between diaphragm thickening fraction with transdiaphragmatic pressure and pressure-time indices were observed.
- In ventilated patients, weak correlations were observed with transdiaphragmatic pressure and none with pressure-time index.
- Ultrasound use to assess diaphragm function should be done with caution.

ABSTRACT

Background: The relationship between the diaphragm thickening fraction and the transdiaphragmatic pressure, the reference method to evaluate the diaphragm function, has not been clearly established. This study investigated the global and intraindividual relationship between the thickening fraction of the diaphragm and the transdiaphragmatic pressure. The authors hypothesized that the diaphragm thickening fraction would be positively and significantly correlated to the transdiaphragmatic pressure, in both healthy participants and ventilated patients.

Methods: Fourteen healthy individuals and 25 mechanically ventilated patients (enrolled in two previous physiologic investigations) participated in the current study. The zone of apposition of the right hemidiaphragm was imaged simultaneously to transdiaphragmatic pressure recording within different breathing conditions, *i.e.*, external inspiratory threshold loading in healthy individuals and various pressure support settings in patients. A blinded offline breath-by-breath analysis synchronously computed the changes in transdiaphragmatic pressure, the diaphragm pressure-time product, and diaphragm thickening fraction. Global and intraindividual relationships between variables were assessed.

Results: In healthy subjects, both changes in transdiaphragmatic pressure and diaphragm pressure-time product were moderately correlated to diaphragm thickening fraction (repeated measures correlation = 0.40, $P < 0.0001$; and repeated measures correlation = 0.38, $P < 0.0001$, respectively). In mechanically ventilated patients, changes in transdiaphragmatic pressure and thickening fraction were weakly correlated (repeated measures correlation = 0.11, $P = 0.008$), while diaphragm pressure-time product and thickening fraction were not (repeated measures correlation = 0.04, $P = 0.396$). Individually, changes in transdiaphragmatic pressure and thickening fraction were significantly correlated in 8 of 14 healthy subjects ($\rho = 0.30$ to 0.85, all $P < 0.05$) and in 2 of 25 mechanically ventilated patients ($\rho = 0.47$ to 0.64, all $P < 0.05$). Diaphragm pressure-time product and thickening fraction correlated in 8 of 14 healthy subjects ($\rho = 0.41$ to 0.82, all $P < 0.02$) and in 2 of 25 mechanically ventilated patients ($\rho = 0.63$ to 0.66, all $P < 0.01$).

Conclusions: Overall, diaphragm function as assessed with transdiaphragmatic pressure was weakly related to diaphragm thickening fraction. The diaphragm thickening fraction should not be used in healthy subjects or ventilated patients when changes in diaphragm function are evaluated.

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The diaphragm acts as a piston within the chest, generating air flow as it descends and displaces the abdominal contents beneath and elevates the lower thorax. The pressure generated across the dome between the thoracic and abdominal cavities, the transdiaphragmatic pressure, is proportional to the tension developed within the muscle fibers.[1] Transdiaphragmatic pressure is commonly used as a surrogate of diaphragm function. Transdiaphragmatic pressure is defined as the difference between esophageal and gastric pressure so that transdiaphragmatic pressure = gastric pressure – esophageal pressure.[2] Measuring transdiaphragmatic

pressure provides useful information in various clinical settings in which diaphragm dysfunction occurs as within the intensive care unit (ICU).[3–8] However, measuring esophageal pressure and gastric pressure relies on the use of gastroesophageal catheters (inserted through the nose or mouth of the patients), which explains why clinicians may be reluctant to use this technique. Alternatively, the diaphragm function can be noninvasively explored by ultrasound. Through an intercostal approach, one can image the muscular layer of the diaphragm surrounded by two hyperechoic layers, *i.e.*, the pleura and peritoneum, at the zone of apposition of the right hemidiaphragm.[9–11] One particular index derived from diaphragm ultrasound is known as the diaphragm thickening fraction. This is calculated based on the change in diaphragm thickness during inspiration,[11] and was first used in 1989 by Wait *et al.*[12] Various studies reported that diaphragm thickening fraction may guide clinicians in evaluating diaphragm function,[13] and in predicting the outcome of weaning in mechanically ventilated patients,[14–17] although the latter point is still debated.[11] Furthermore, several authors have suggested that diaphragm thickening fraction may reflect the diaphragm function. Goligher *et al.*[18] reported the relationship between the changes in transdiaphragmatic pressure and diaphragm thickening fraction in five healthy subjects. Although statistically significant, the authors noted large variability in diaphragm thickening fraction for a given change in transdiaphragmatic pressure. Similarly, Umbrello *et al.*[19,20] and Vivier *et al.*[21] showed that esophageal and diaphragm pressure-time product were significantly related to diaphragm thickening fraction with also large differences in diaphragm pressure-time product values for a given diaphragm thickening fraction value. This variability may arise from interindividual differences in the change in transdiaphragmatic pressure–diaphragm thickening fraction and diaphragm pressure-time product–diaphragm thickening fraction relationships, which were not accounted for in the aforementioned studies. By contrast, Oppersma *et al.*[22] found no increase in diaphragm thickening fraction during stepwise increase in inspiratory efforts from 0 to 50% of maximal inspiratory pressure in healthy subjects. However, the aforementioned studies reported relationships between diaphragm function and diaphragm thickening fraction based on averaged data for a given ventilation condition, thus ignoring change in transdiaphragmatic pressure and diaphragm thickening fraction variability within the condition of ventilation tested and its impact on the change in the transdiaphragmatic pressure–diaphragm thickening fraction relationship. A breath-by-breath analysis may allow us to better understand such relationships. Also, assessing the relationship between diaphragm thickening fraction and diaphragm function at the patient level, instead of grouping patients altogether, could explain the high variability in diaphragm thickening fraction observed in these previous works. In addition, diaphragm thickening fraction has been reported to vary as much as 27%.[18] This moderate reliability may affect the strength of its relationship with diaphragm function as assessed using transdiaphragmatic pressure.[18] Taken together, these results emphasize that the relationship between diaphragm function and diaphragm thickening fraction requires further investigation. Therefore, the objective of the study was to examine the within-individual relationship between change in transdiaphragmatic pressure and diaphragm thickening fraction in healthy subjects and mechanically ventilated patients. By performing a breath-by-breath analysis, we hypothesized that diaphragm thickening fraction would be positively and significantly correlated to change in transdiaphragmatic pressure and diaphragm pressure-time product.

Materials and Methods

The current study includes participants from two previously published studies[23,24] registered on ClinicalTrial.gov (NCT03313141 and NCT03832231) and approved by local ethics committees (registration numbers: 2015-A00949-40 and 2018-A022311-54). We used data prospectively collected during these two physiologic studies that were primarily designed to investigate a new ultrasound technology (transient shear wave elastography).[23,24] In the current work, a *post hoc* analysis of unpublished data pertaining to diaphragm thickness and thickening fraction is reported. Written informed consent was obtained from all participants or their relatives. The studies followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

All participants had to be older than 18 yr at the time of inclusion. Healthy subjects were free from any disease and nonsmokers. Mechanically ventilated patients had been intubated and ventilated for a minimum of 24 h, and failed a first spontaneous breathing trial. They could be included if they met the following readiness-to-wean criteria[25]: arterial oxygen saturation greater than 90% or Pao_2/fraction of inspired oxygen 150 mmHg or greater with a fraction of inspired oxygen 40% or less, no or minimal vasopressor, and positive end-expiratory pressure (PEEP) 8 cm H_2O or lower. Patients under a legal protection measure, with

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known allergies to anesthetizing, pregnant, or with a contraindication to the insertion of a gastroesophageal probe were not included.

Flow and Pressure Measurements

Different apparatus were used in healthy subjects and mechanically ventilated patients. In healthy subjects, two 8-cm balloon catheters (C76080U; Marquat Génie Biomédical, France), connected separately to differential pressure transducers (DP45-32; Validyne, USA), were used to measure esophageal pressure and gastric pressure. For flow measurement, healthy subjects wore a nose clip and were breathing through a mouthpiece, itself connected to a two-way valve and pneumotachograph (3700 series; linearity range, 0 to 160 $l \cdot min^{-1}$; Hans Rudolph, USA). Flow and pressure signals were digitized (Powerlab; ADInstruments, Australia) and recorded at a sampling frequency of 2 kHz (Labchart; ADInstruments). In mechanically ventilated patients, the flow was measured using a flow sensor (Hamilton Medical, Switzerland) connected to a spirometer (ADInstruments). A double-balloon feeding catheter (NutriVentTM; Mirandola, Italy), connected to differential pressure transducers (DP45-32; Validyne), allowed the recording of esophageal pressure and gastric pressure. Flow and pressure signals were digitized (Powerlab) and recorded at a sampling frequency of 1 kHz (Labchart). A dynamic occlusion test was performed to validate esophageal balloon position, allowing the visualization of a corresponding negative deflection in esophageal pressure and airway pressure during inspiratory effort.[26] To validate gastric balloon position, an increase in gastric pressure had to be observed when gently pressing the patient's abdomen. In both settings, transdiaphragmatic pressure was continuously obtained by the online subtraction of esophageal pressure from gastric pressure.

Ultrasound Imaging

In healthy subjects and patients, the zone of apposition of the right hemidiaphragm was imaged using the same linear transducer array (7 to 10 MHz; SL10-2; Supersonic Imagine, France) driven by an ultrasound scanner (Aixplorer; Supersonic Imagine). The diaphragm was imaged through the intercostal approach, with the probe placed on the 8th to 10th intercostal space near the midaxillary line. A generous amount of gel was applied to the participant's skin to optimize acoustic coupling. The diaphragm was identified as a muscular layer in-between two hyperechoic lines (*i.e.*, the pleura and peritoneum), superficial to the liver. Probe location was skin-marked as it is known to increase the reproducibility of diaphragm thickening fraction measurement.[18] Ultrasound measurements were performed by a single trained-operator in healthy subjects (M.D.) and mechanically ventilated patients (Q.F.). Both operators had extensive experience in diaphragm ultrasound imaging and followed the aforementioned methodology to ensure the reliability of ultrasound recordings across participants and allow an accurate comparison of healthy subjects and mechanically ventilated patients.

Protocol

All participants (healthy and patients) were in a semirecumbent position throughout the entire protocol.

Healthy Subjects. Healthy subjects first performed a maximal isovolumetric inspiratory effort (Müller maneuver[27]) to determine their maximal transdiaphragmatic pressure and maximal inspiratory pressure at functional residual capacity. Briefly, participants were asked to perform maximal inspiratory efforts using a unidirectional valve allowing expiration only. At least five trials were performed, and trials were repeated until three reproducible (less than 10% variance) trials were recorded. They then went through a randomized series of stepwise inspiratory threshold loading from 10 to 50% of maximal inspiratory pressure, with 10% steps. As previously described,[22,23] the inspiratory threshold loading was applied using an in-house developed apparatus modified from Chen *et al.*,[28] generating a constant negative pressure that the subjects had to overcome. Participants were instructed to exert an outward motion of the abdomen during each inspiration, as this breathing technique optimizes diaphragm recruitment.[29] Each loading task was repeated twice with at least six respiratory cycles per recording. Participants were receiving visual feedback of their effort to ensure they reach the desired inspiratory pressure target.

Mechanically Ventilated Patients. In mechanically ventilated patients, recordings were performed under different conditions of ventilation. Patients were ventilated under pressure support ventilation mode. Four conditions of ventilation were applied in a randomized order: (1) initial ventilator settings predefined by the attending physician, (2) pressure support increased by 25% with baseline PEEP, (3) pressure support decreased by 25% with baseline PEEP, and (4) baseline pressure support and zero end-expiratory pressure. Each breathing condition was maintained for 10 min with 30-s acquisitions performed at 3 and 9 min within the condition. Eventually, recordings were performed during spontaneous breathing, where no assistance from the ventilator was provided. During this maneuver, patients were still connected to the ventilator, but pressure support and PEEP were set to 0 cm H_2O. Maximal transdiaphragmatic pressure was measured during a Müller maneuver to assess maximal diaphragm function. Patients were briefly disconnected from the ventilator and attached to a one-way valve allowing expiration only. The occlusion was maintained for at least 20 s but not longer than 30 s, during which subsequent efforts of gradual intensity were recorded until a plateau in change in transdiaphragmatic pressure was observed. Patients were then immediately reconnected to the ventilator. Patients were conscious and did not receive sedatives, while a light dose of analgesics was allowed.

Data Analysis

A controlling computer was used to trigger simultaneously the recording of the physiologic signals (airway pressures, esophageal and gastric pressure) and ultrasound images. As a result during the offline analysis process, a given diaphragm thickening fraction value could be directly compared to the change in transdiaphragmatic pressure of the same respiratory cycle. An overview of the setup, along with the acquired physiologic and ultrasound parameters as well as the calculated variables, are displayed in figure 1. Data were analyzed offline using MATLAB (MathWorks, USA) scripts developed in-house. The offline analysis was performed by an operator blinded to the participant's identity and condition of ventilation. As previously reported,[24] relying on the flow signal to demarcate respiratory cycles may mask the onset of inspiratory effort, especially in mechanically ventilated patients who need to overcome intrinsic PEEP.[30,31] For this reason, the operator delimited each respiratory cycle by visually identifying the negative deflection in esophageal pressure associated with an increase in flow and gastric pressure. Change in transdiaphragmatic pressure was computed as the difference between the start of the increase in transdiaphragmatic pressure and the positive peak value of transdiaphragmatic pressure during inspiration. Diaphragm pressure-time product per breath was computed as the area under the transdiaphragmatic pressure curve during the neural inspiratory time.[32] Diaphragm pressure-time product per minute was calculated as the product between diaphragm pressure-time product and respiratory rate for a given breathing condition. Maximum transdiaphragmatic pressure was calculated as the difference between transdiaphragmatic pressure at functional residual capacity and maximal transdiaphragmatic pressure during the Müller maneuver. For each breathing cycle, the Gilbert index (change in gastric pressure / change in transdiaphragmatic pressure)[33] was calculated in order to quantify diaphragm contribution to inspiratory effort. A higher index indicates higher diaphragm contribution to inspiratory effort.[34]

For every recording, a time-motion (M-mode) image was generated, on top of which the onset and end of inspiration for a given cycle were plotted (fig. 1). Subsequently, an experimented operator (T.P.), blinded to the condition of ventilation and participant identity, manually positioned a vertical electronic caliper at the internal border of the pleura and peritoneum membranes. Diaphragm thickness at

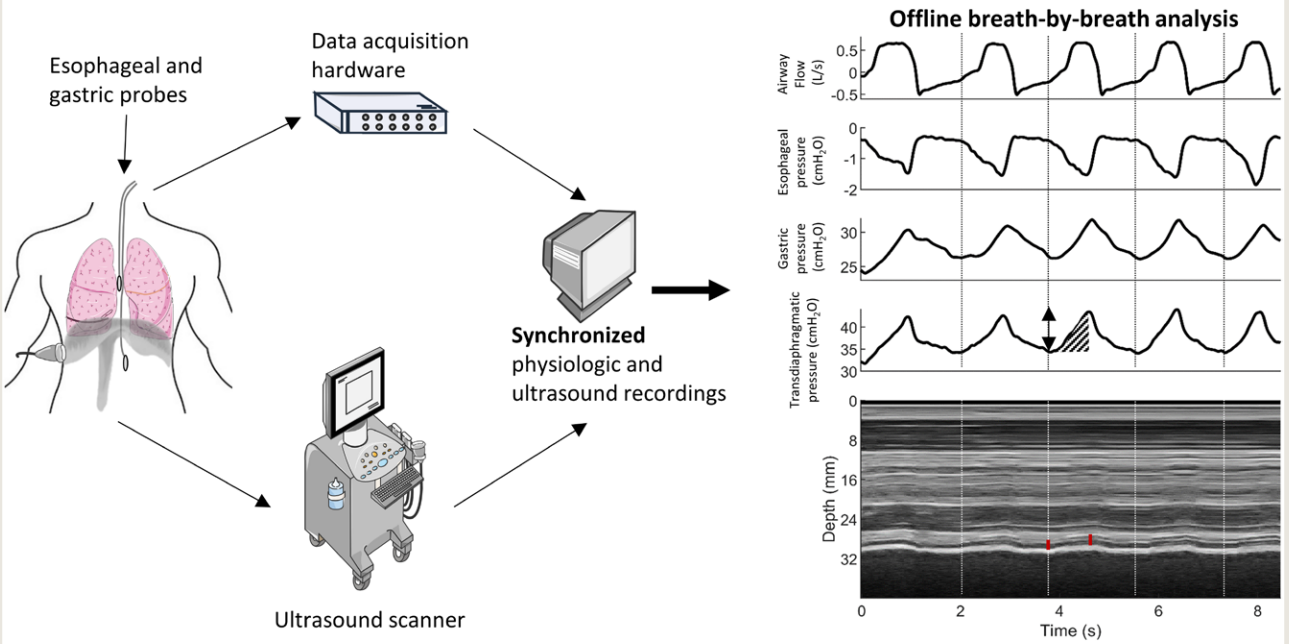

Fig. 1. Experimental setup used to synchronize the physiologic parameters with the ultrasound recordings. The physiologic and ultrasound recordings were simultaneously acquired using a controlling computer triggering both recordings. All data were then saved on the controlling computer in order to perform the offline blinded analysis. Changes in transdiaphragmatic pressure (*vertical double arrow*) were computed as the difference between the start of the increase in transdiaphragmatic pressure and the positive peak value of transdiaphragmatic pressure during inspiration. Transdiaphragmatic pressure-time product per breath (*hatched area*) was calculated as the area under the transdiaphragmatic pressure curve during the neural inspiratory time. For each respiratory cycle, delimited by the *vertical dotted lines*, diaphragm thickness at end expiration and at peak inspiration were manually measured (*red vertical lines*). Diaphragm thickening fraction was defined as the percentage change between diaphragm thickness at end expiration and diaphragm thickness at peak inspiration.

end-expiration ($T_{di,ee}$) and peak inspiration ($T_{di,pi}$, *i.e.*, maximal diaphragm thickness during inspiration) were defined as the distance between the internal border of the pleura and peritoneum membranes. Diaphragm thickening fraction (TFdi) was defined as the percentage change between $T_{di,ee}$ and $T_{di,pi}$, such that

$$\text{TFdi (\%)} = \frac{T_{di,pi} - T_{di,ee}}{T_{di,ee}} \times 100 \quad (1)$$

Recordings of mechanically ventilated patients were potentially affected by cough and body movement inferring with transdiaphragmatic pressure and ultrasound recordings. For this reason, the three cycles with the least variation in change in transdiaphragmatic pressure were considered as representative of a given ventilatory condition and selected for further analysis.[24] Asynchronous breaths, define as a mismatch between patient's effort and the ventilator, were excluded from the analysis. In healthy subjects, cycles that were affected by cough or poor image quality were discarded. In both populations, breathing cycles for which any data were missing or not measurable were discarded so that a complete case analysis could be performed.

Statistical Analysis

Descriptive statistics are expressed as median (25th to 75th percentile) unless stated otherwise. Since we used data pertaining to patients enrolled in two previous studies,[23,24] we estimated the sample size *a posteriori*. We calculated that at least 13 patients were needed to demonstrate a correlation of 0.70 between change in transdiaphragmatic pressure and diaphragm thickening fraction. All statistical analyses were two-tail tested. Repeated measures correlation (95% CI) was computed to determine overall change in transdiaphragmatic pressure–diaphragm thickening fraction and diaphragm pressure-time product–diaphragm thickening fraction relationships, using the 'rmcorr' R package.[35] This technique accounts for the interindividual variability and the independence of repeated measures between individuals. Within-individual relationships were assessed using the nonparametric Spearman correlation coefficient (ρ), as variables failed the Shapiro–Wilk normality test. Spearman correlation coefficients were calculated using the base R "cor.test" function. A mixed effect model was run to examine the Gilbert index × diaphragm thickening fraction interaction effect on change in transdiaphragmatic pressure using the "lme4" package in R.[36] If a significant interaction effect was found, repeated measure correlations were computed for breaths with a Gilbert index greater than 0.3 and for breaths with a Gilbert index less than 0.3.[37] Reproducibility of diaphragm thickening fraction, change in transdiaphragmatic pressure, and diaphragm pressure-time product were assessed through each breathing condition by calculating standard errors of measurement and intraclass correlation coefficients to report absolute and relative reliability, respectively.[38] Analyses were performed separately in healthy participants and patients. Analyses were performed in the computing environment R.[39] Significance was set at $P < 0.05$ for all tests.

Results

Population

Fourteen healthy subjects and 25 mechanically ventilated patients were studied. Table 1 presents the characteristics of participants at inclusion. ICU patients had been ventilated for 4 (3 to 7) days and were receiving a pressure support level of 10 (9 to 13) cm H_2O and a PEEP level of 5 (5 to 5) cm H_2O. In mechanically ventilated patients, 3,878 respiratory cycles were recorded, and 815 were considered for the analysis (*i.e.*, corresponding to the three respiratory cycles with the least variation in change in transdiaphragmatic pressure). Of those, 383 were withdrawn from the analysis because of poor image quality, cough, expiratory muscle recruitment during previous expiration, or patient movement. In healthy subjects, 813 cycles were recorded, and 129 were discarded because of poor image quality, body movement, or lung artefact. Eventually, a total of 684 and 587 respiratory cycles were analyzed for healthy subjects and mechanically ventilated patients, respectively. Maximal transdiaphragmatic pressure was 119 (108 to 142) cm H_2O in healthy subjects and 24 (15 to 35) cm H_2O in mechanically ventilated patients.

Group-level Relationship between Diaphragm Thickening Fraction and Diaphragm Function

Diaphragm thickening fraction, change in transdiaphragmatic pressure, and diaphragm pressure-time product at all ventilatory conditions in mechanically ventilated patients are presented in figure 2. Likewise, figure 3 displays diaphragm thickening fraction, change in transdiaphragmatic

Table 1. Participants' Characteristics at Inclusion

Characteristics	Values
Healthy subjects	N = 14
Age, yr	32 (24–38)
Women, n (%)	4 (29%)
Body mass index, kg · m^{-2}	22 (21–25)
Maximal transdiaphragmatic pressure, cm H_2O	119 (108–142)
Mechanically ventilated patients	N = 25
Age, yr	65 (57–77)
Women, n (%)	5 (20%)
Body mass index, kg · m^{-2}	25 (21–27)
Maximal transdiaphragmatic pressure, cm H_2O	24 (15–35)
Duration of intubation, days	4 (3–7)
Pressure support, cm H_2O	10 (9–13)
Positive end-expiratory pressure, cm H_2O	5 (5–5)
Fraction of inspired oxygen, %	30 (30–40)

Data are presented as median (25th to 75th percentile) or as number (%).

pressure, and diaphragm pressure-time product at all inspiratory loads in healthy subjects. Diaphragm thickening fraction significantly correlated with change in transdiaphragmatic pressure in healthy subjects (repeated measures correlation = 0.40; 95% CI, 0.34 to 0.47; $P < 0.0001$) and in mechanically ventilated patients

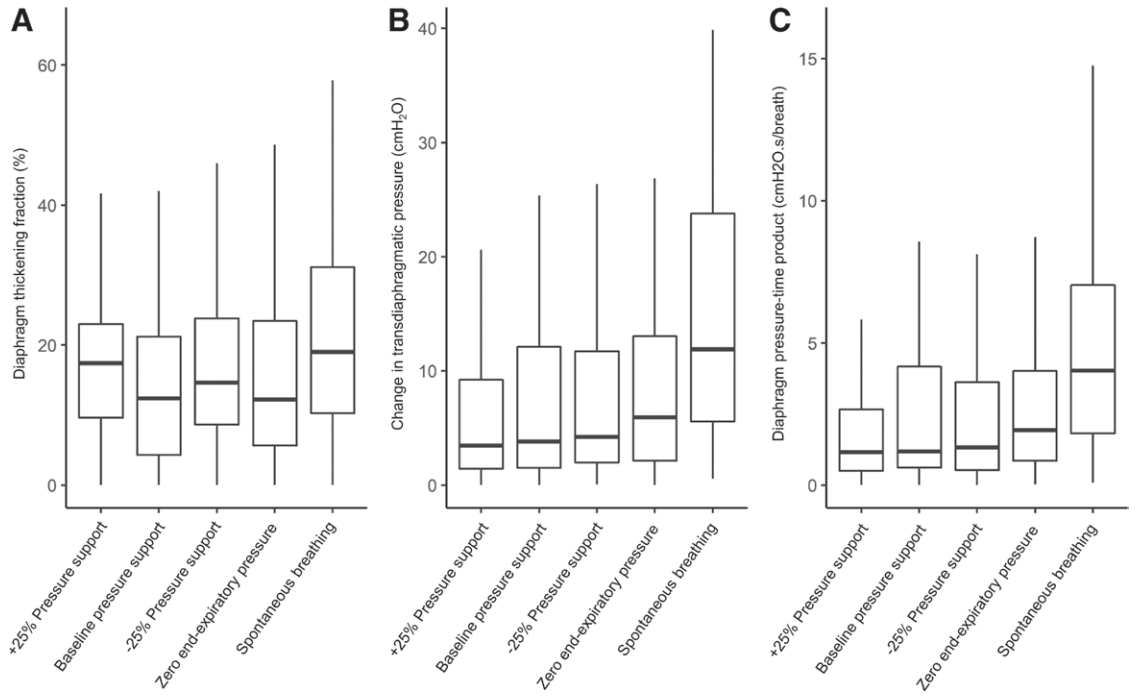

Fig. 2. Diaphragm thickening fraction (*A*), changes in transdiaphragmatic pressure (*B*), and diaphragm pressure-time product per breath (*C*) according to the condition of ventilation in mechanically ventilated patients. *Box plots* display the median and interquartile range. *Whiskers* represent the range.

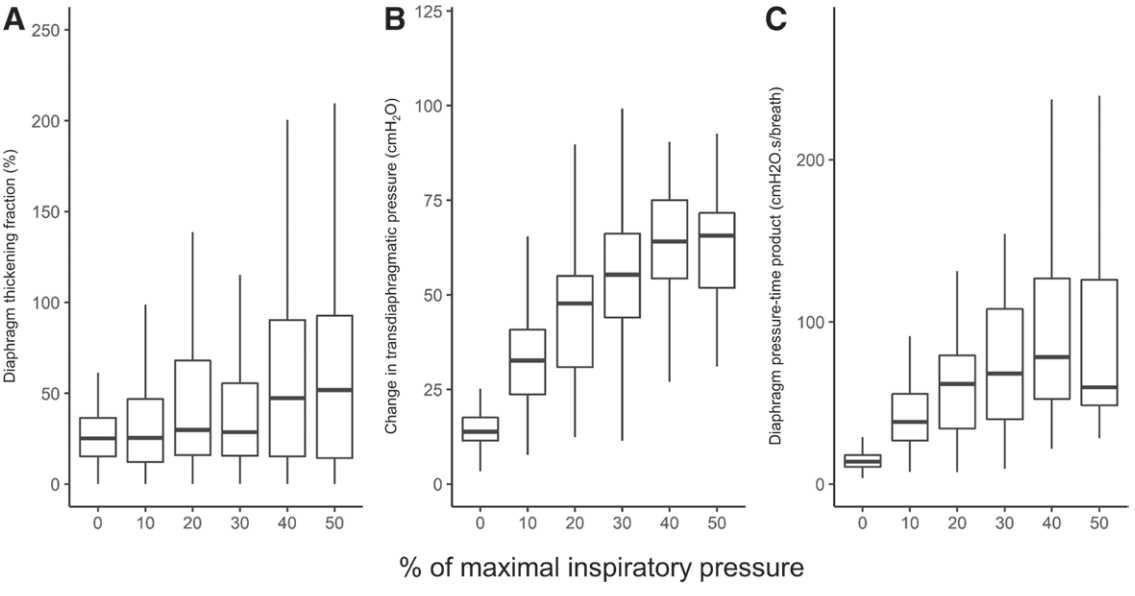

Fig. 3. Diaphragm thickening fraction (*A*), changes in transdiaphragmatic pressure (*B*), and diaphragm pressure-time product per breath (*C*) according to the inspiratory load in healthy subjects. *Box plots* display the median and interquartile range. *Whiskers* represent the range.

(repeated measures correlation = 0.11; 95% CI, 0.03 to 0.19; $P = 0.008$). Regarding diaphragm thickening fraction–diaphragm pressure-time product relationships, a significant relationship was found at the group level in healthy subjects (repeated measures correlation = 0.38; 95% CI, 0.31 to 0.44; $P < 0.0001$) but not in mechanically ventilated patients (repeated measures correlation = 0.04; 95% CI, –0.05 to 0.12; $P = 0.396$). Group-level relationships between diaphragm thickening fraction and change in transdiaphragmatic pressure, and between diaphragm thickening fraction and diaphragm pressure-time product, are shown in figures 4 and 5, respectively.

Within-individual Relationships between Diaphragm Thickening Fraction and Diaphragm Function

Individual relationship, including all data points, between diaphragm thickening fraction and change in transdiaphragmatic pressure, and between diaphragm thickening fraction and diaphragm pressure-time product, are presented in Supplemental Digital Content, figures SDC1 to SDC4 (http://links.lww.com/ALN/C739). Individual correlations between diaphragm thickening fraction and change in transdiaphragmatic pressure were significant in eight (57%) healthy subjects ($\rho = 0.30$ to 0.85; all $P < 0.05$)

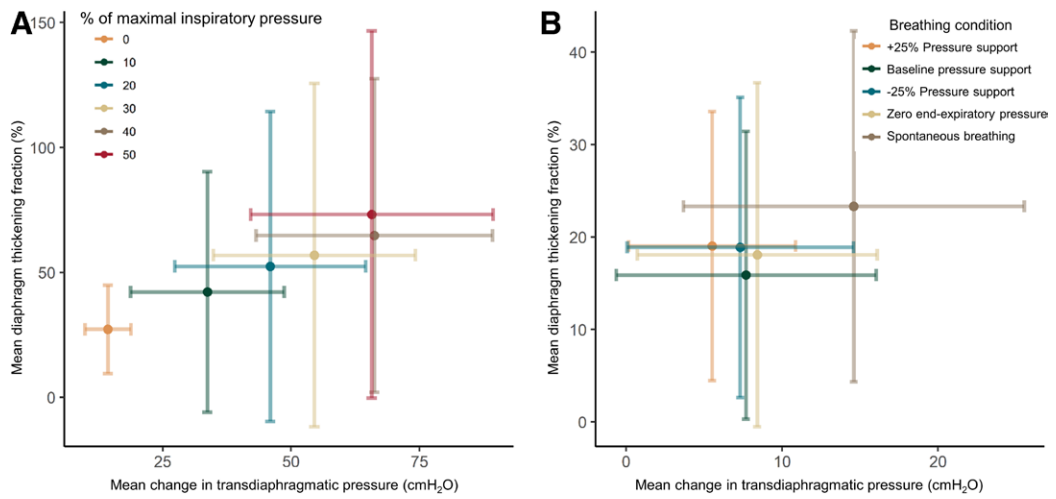

Fig. 4. Group level relationships between diaphragm thickening fraction and changes in transdiaphragmatic pressure in healthy subjects (*A*) and in mechanically ventilated patients (*B*). Data are presented as mean ± SD.

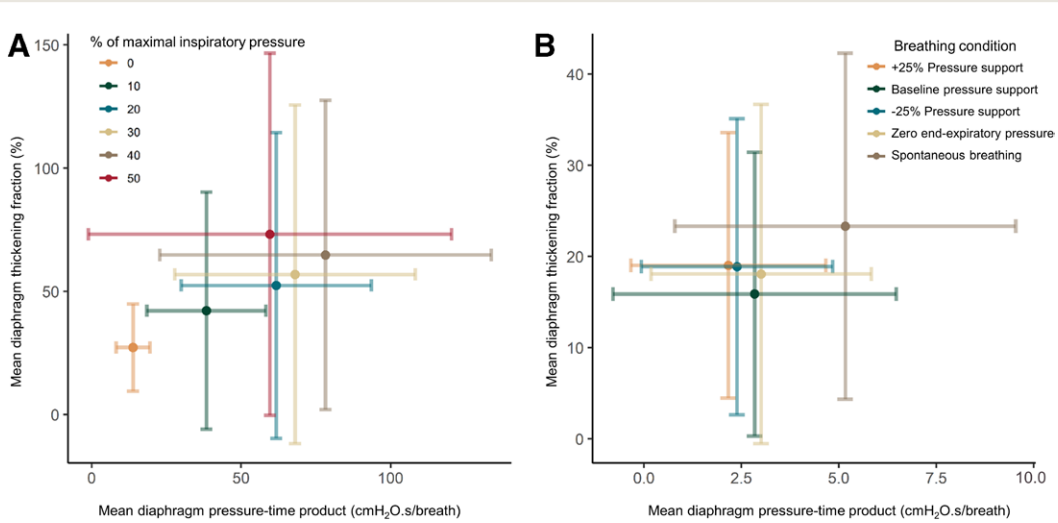

Fig. 5. Group level relationships between diaphragm thickening fraction and diaphragm pressure-time product in healthy subjects (*A*) and in mechanically ventilated patients (*B*). Data are presented as mean ± SD.

and in two (8%) mechanically ventilated patients ($\rho = 0.47$ to 0.64; all $P < 0.05$). Individual diaphragm thickening fraction–diaphragm pressure-time product relationship was significant in eight (57%) healthy subjects ($\rho = 0.28$ to 0.84; all $P < 0.05$) and in two (8%) mechanically ventilated patients ($\rho = 0.63$ to 0.66; all $P < 0.01$). Table 2 displays the overall results of the relationships between diaphragm thickening fraction and change in transdiaphragmatic pressure and between diaphragm thickening fraction and diaphragm pressure-time product. Supplemental Digital Content tables SDC1 and SDC2 (http://links.lww.com/ALN/C739) present the standard error of measurement and intraclass correlation coefficients of diaphragm thickening fraction, change in transdiaphragmatic pressure, and diaphragm pressure-time product across breathing conditions in healthy subjects and mechanically ventilated patients, respectively.

Diaphragmatic Contribution to Inspiratory Work

In healthy subjects, the mixed models did not reveal a significant interaction effect of the Gilbert index and diaphragm thickening fraction on change in transdiaphragmatic pressure ($\beta = 0.02$; $P = 0.648$). In patients, a significant and negative interaction effect of the Gilbert index and diaphragm thickening fraction was found on change in transdiaphragmatic pressure ($\beta = –0.27$; $P < 0.001$). Repeated measures correlation between change in transdiaphragmatic pressure and diaphragm thickening fraction was not significant for breaths with a Gilbert index greater than 0.3 (repeated measures correlation = 0.08; 95% CI, –0.06 to 0.22; $P = 0.255$), but was significant for breaths with a Gilbert index less than 0.3 (repeated measures correlation = 0.18; 95% CI, 0.08 to 0.28; $P < 0.001$).

Discussion

This study investigated the relationship between simultaneously recorded diaphragm thickening fraction and diaphragm pressure production, both in healthy subjects and in mechanically ventilated patients. Our results indicate that, at the group level, significant change in transdiaphragmatic pressure–diaphragm thickening fraction relationships exist in both populations, although the fact that they were only moderate in healthy subjects and weak in mechanically ventilated patients hampered the possibility of inferring pressure output from ultrasound recordings. Diaphragm pressure-time product–diaphragm thickening fraction relationships exist in healthy subjects only. When considering the intraindividual relationship between diaphragm thickening fraction and diaphragm function, a significant relationship was found in approximately 50% of healthy subjects and in less than 10% of mechanically ventilated patients.

Diaphragm thickening fraction is the magnitude of the increase in diaphragm thickness during inspiration.[11] Several authors showed that diaphragm thickening fraction increased with lung volumes,[12,40,41] suggesting a relationship between diaphragm thickening fraction and the intensity of diaphragm contraction. However, despite its extensive use in the ICU,[3,10,11] little is known about the extent to which diaphragm thickening fraction may reflect the transdiaphragmatic pressure—that is, the physiologic estimate of the diaphragm function.[42] Very few studies reported correlation values for the diaphragm thickening fraction–change in transdiaphragmatic pressure relationship.[18,22] Goligher *et al.*[18] reported a significant diaphragm thickening fraction–change in transdiaphragmatic pressure correlation from five pooled healthy subjects. On the other hand, Oppersma *et al.*[22] showed no effect of stepwise increase of inspiratory load on the change in diaphragm thickening fraction. Our results show that, at the group level, diaphragm thickening fraction was significantly correlated to change in transdiaphragmatic pressure in healthy participants. Nonetheless, one should note the moderate power of this relationship (*i.e.*, repeated measures correlation = 0.40). This result confirms previous findings that found either a weak correlation between diaphragm thickening fraction and change in transdiaphragmatic pressure[18] or no correlation at all.[22] Also, high interindividual variability in diaphragm thickening fraction was found for a given change in transdiaphragmatic pressure value, which may explain the moderate correlation found in healthy subjects (*i.e.*, repeated measures correlation = 0.40). Although significant, the relationship between diaphragm

Table 2. Correlations between Diaphragm Thickening Fraction and Indices of Diaphragm Function

	Healthy Subjects	Mechanically Ventilated Patients
Change in transdiaphragmatic pressure–diaphragm thickening fraction relationship		
Group-level relationship	Repeated measures correlation = 0.40, $P < 0.001$	Repeated measures correlation = 0.11, $P = 0.007$
Within-individual relationship	$\rho = –0.44$ to 0.85	$\rho = –0.47$ to 0.64
Individuals with a significant correlation, n (%)	8 (57%)	2 (8%)
Diaphragm pressure-time product–diaphragm thickening fraction relationship		
Group-level relationship	Repeated measures correlation = 0.38, $P < 0.001$	Repeated measures correlation = 0.04, $P = 0.396$
Within-individual relationships	$\rho = –0.29$ to 0.84	$\rho = –0.42$ to 0.66
Individuals with a significant correlation, n (%)	8 (57%)	2 (8%)

Repeated measures correlations were measured to assess group-level correlations. Spearman correlation coefficients were calculated to determine within-individual correlations.

thickening fraction and change in transdiaphragmatic pressure was very weak in mechanically ventilated patients at the group level (repeated measures correlation = 0.11). Several factors may explain this finding. First, mechanically ventilated patients exhibited a much narrower range of change in transdiaphragmatic pressure values (0 to 40 cm H_2O) as compared to healthy subjects (0 to 120 cm H_2O). This may result in subtle changes in diaphragm function that diaphragm thickening fraction may be not able to detect. Second, it cannot be ruled out that inspiratory work is redistributed across the various inspiratory muscles,[29] which may partially explain the high interindividual variability of diaphragm thickening fraction.[43] This point highlights that transdiaphragmatic pressure does not solely depend on diaphragm activation,[44] while diaphragm thickening fraction does. Besides change in transdiaphragmatic pressure, diaphragm pressure-time product is a common index of diaphragm function. Other studies investigated the relationships between diaphragm pressure-time product and diaphragm thickening fraction on pooled data at the group level. For instance, Vivier *et al.*[21] reported a significant diaphragm pressure-time product–diaphragm thickening fraction correlation ($\rho = 0.74$; $P < 0.001$) in noninvasively ventilated patients. Likewise, Umbrello *et al.*[19] reported similar results in mechanically ventilated patients ($r = 0.70$; $P < 0.001$). Our findings partially support these studies, as diaphragm pressure-time product–diaphragm thickening fraction relationship at the group level was significant in healthy subjects only. However, this relationship was not significant in mechanically ventilated patients. As illustrated in figure 2, very little variation in diaphragm function was observed when varying ventilator settings in patients. This may partly explain why little to no change was observed in diaphragm thickening fraction from one condition of ventilation to another in this context, whereas another study reported a significant change in diaphragm thickening fraction in recently extubated patients, presumably characterized by high respiratory resistances.[21] Here again, the fact that the range of diaphragm pressure-time product was much wider in healthy subjects (3 to 279 cm $H_2O \cdot$ s/breath) than in mechanically ventilated patients (0 to 22 cm $H_2O \cdot$ s/breath), coupled with a possible redistribution of the inspiratory work across inspiratory muscles, may partially explain why the diaphragm thickening fraction–diaphragm pressure-time product relationship was not significant in patients. Also, it must be noted that, contrary to change in transdiaphragmatic pressure and diaphragm thickening fraction, diaphragm pressure-time product is time-dependent. This means that the correlation between diaphragm pressure-time product and diaphragm thickening fraction relies not only on the level of transdiaphragmatic pressure but also on the inspiratory time. This may contribute to explaining the weak correlation between the two parameters.

Group-level analyses provide a broad picture of the relationship between two variables. However, they do not account for the interindividual variability, which could partly explain the difference in change in transdiaphragmatic pressure or diaphragm pressure-time product for a given diaphragm thickening fraction value. For this reason, we also performed a breath-by-breath analysis of the relationship between diaphragm thickening fraction and physiologic indices of diaphragm function. By doing so, we were able to investigate the direct link between the change in transdiaphragmatic pressure during a respiratory cycle and the diaphragm thickening fraction for the very same respiratory cycle. To the best of our knowledge, this is the first study to conduct such an analysis. We found that intraindividual change in transdiaphragmatic pressure–diaphragm thickening fraction relationships were significant in eight (57%) healthy subjects and two (8%) mechanically ventilated patients. Accordingly, our findings suggest caution when using diaphragm thickening fraction as a surrogate of transdiaphragmatic pressure. Also, one must note that high intraindividual diaphragm thickening fraction variability was observed for a given change in transdiaphragmatic pressure, even in participants exhibiting a significant change in transdiaphragmatic pressure–diaphragm thickening fraction relationship. The slope of the relationship between change in transdiaphragmatic pressure and diaphragm thickening fraction greatly differed from one participant to another, even when a significant correlation was found between the two parameters. Supplemental Digital Content figure SDC5 (http://links.lww.com/ALN/C739) illustrates the change in transdiaphragmatic pressure–diaphragm thickening fraction relationship in two participants with a significant correlation but distinct relationship slope. Likewise, seven healthy subjects and two mechanically ventilated patients presented with a significant diaphragm pressure-time product–diaphragm thickening fraction relationship. There are several possible explanations for these results. Change in transdiaphragmatic pressure is not an actual force but rather the pressure change resulting from diaphragm contraction. Indeed, as the diaphragm contracts, its caudal displacement increases gastric pressure, which acts as a reacting pressure to this caudal displacement.[45] In turn, different abdominal conformations would result in different gastric pressure reactions for a given diaphragm force production.[44] Also, and as already mentioned in this discussion, intercostal and neck inspiratory muscles may be responsible for a partial increase in the swing of esophageal pressure during inspiration, which would impact change in transdiaphragmatic pressure without affecting diaphragm thickening fraction. One may also question whether the zone imaged is representative of the whole diaphragm. Previous research showed that the zone of apposition is the region of the diaphragm displaying the highest amount of active shortening.[46] Nonetheless, it cannot be ruled out that the force generated by the diaphragm may not be uniform across the muscle, particularly in patients.[47] In such cases, imaging the zone of apposition may be inadequate to monitor diaphragm function. Finally, another source of uncertainty lies in the fact that diaphragm thickening fraction depends on the manual measurement of diaphragm thickness. Goligher *et al.*[18] showed that

diaphragm thickening fraction was moderately repeatable, with an intraoperator variability of 16%. Our results suggest that diaphragm thickening fractions across respiratory cycles recorded in a given breathing condition are moderately to highly reliable, as demonstrated with intraclass correlation coefficients ranging between 0.71 and 0.93 (Supplemental Digital Content tables SDC1 and SDC2, http://links.lww.com/ALN/C739). Nonetheless, standard error of measurement for diaphragm thickening fraction varied from 10 to 29% in healthy subjects and from 8 to 11% in mechanically ventilated patients, supporting previous studies reporting moderate repeatability of diaphragm thickening fraction.[18] Both in healthy subjects and in mechanically ventilated patients, we carefully skin-marked the position of the probe to ensure consistent imaging across trials. In addition, a single operator proceeded to the measurement of diaphragm thickening fraction as between-operator variability is higher than within-operator variability.[18] Taken altogether, these factors may explain why change in transdiaphragmatic pressure–diaphragm thickening fraction or diaphragm pressure-time product–diaphragm thickening fraction relationships were not significant in a majority of participants.

The Gilbert index is commonly used to determine the diaphragmatic contribution to total inspiratory work.[34] Our mixed model analysis showed that there was a negative and significant interaction effect of the Gilbert index and diaphragm thickening fraction on change in transdiaphragmatic pressure. This means that diaphragm thickening fraction increases less and less as the Gilbert index increases. In other words, additional diaphragmatic contribution to inspiratory effort results in smaller and smaller increases in diaphragm thickening fraction. When stratifying our correlation analysis between breaths with a Gilbert index greater than 0.3 and breaths with a Gilbert index less than 0.3,[37] we showed that the repeated measures correlation was significant only for breaths with a Gilbert index less than 0.3. Three main factors can explain such findings. First, the different correlations may be simply related to the low number of breathing cycles with a Gilbert index greater than 0.3 (n = 221) as compared to breaths with a Gilbert index less than 0.3 (n = 363). Second, the range of change in transdiaphragmatic pressure and diaphragm thickening fraction was substantially greater for cycles with a Gilbert index less than 0.3 compared to cycles with a Gilbert index greater than 0.3 (0 to 40 cm H_2O *vs.* 0 to 20 cm H_2O for change in transdiaphragmatic pressure and 0 to 98% *vs.* 0 to 73% for diaphragm thickening fraction, respectively). Third, the low, albeit significant, interaction effect of the Gilbert index and diaphragm thickening fraction on change in transdiaphragmatic pressure is not powerful enough, restricting diaphragm thickening fraction ability to detect an increase in diaphragmatic contribution to inspiratory work.

Strengths and Limitations

This work performed a breath-by-breath analysis of the diaphragm thickening fraction and transdiaphragmatic pressure prospectively collected during two previously published studies investigating the use of transient shear wave elastography to evaluate the diaphragm function. By synchronizing ultrasound images with the physiologic signals, we were able to perform a straightforward comparison of diaphragm thickening fraction and other indices of diaphragm function such as diaphragm pressure-time product. Data were analyzed offline, with the operator blinded to the condition of ventilation and participant identity, using standardized scripts allowing repeatable analysis across respiratory cycles. This study has several limitations. The first limitation is inherent to diaphragm thickening fraction measurement, which is its moderate repeatability,[18] although high care was taken to limit its impact on diaphragm thickening fraction measurement. One should note that the correlation between two variables depends on the reliability of the correlated variables.[48] The poor relationship between diaphragm thickening fraction and diaphragm function can therefore be related to the absence of a relationship with diaphragm function, but also to the moderate reliability of its measurement. Therefore, the lower relationship between diaphragm thickening fraction and diaphragm function in patients compared to healthy subjects may be partially attributed to the lower intraclass correlation coefficients of diaphragm thickening fraction in patients (Supplemental Digital Content, tables SDC1 and SDC2, http://links.lww.com/ALN/C739). In addition, potential bias may have influenced the measured correlations. One of them is the cycle selection in mechanically ventilated patients. Although we ensured that the selected cycles were representative of a given ventilatory condition, the observed relationships might slightly differ if different breathing cycles had been analyzed. For instance, cycle selection might have limited the range of change in transdiaphragmatic pressure and diaphragm thickening fraction measured, which would ultimately affect the relationship between these variables. Various factors may also influence the magnitude of a relationship between two variables, such as the variability of the data.[49] As previously stated, the range of change in transdiaphragmatic pressure and diaphragm pressure-time product measured in patients was much narrower as compared to healthy subjects, which could partially explain why the relationships between diaphragm thickening fraction and diaphragm function were weaker in patients. Still, these data represent what ICU clinicians are faced with, and we reason this work could clear up the importance that should be given to diaphragm thickening fraction when used for gauging diaphragm effort. Finally, we solely imaged the right hemidiaphragm, but previous studies reported that extradiaphragmatic inspiratory muscles, such as the parasternal intercostal muscles, also thicken during inspiration in healthy subjects[50] and mechanically ventilated patients.[42] Because some individuals naturally excessively use their accessory inspiratory muscles,[29] a sonographic evaluation of these accessory muscles may improve our understanding of the relationship between inspiratory muscle thickening and diaphragm function.

Generalization of Findings

These findings have important implications in various research and clinical settings involving routine diaphragm monitoring. Because diaphragm thickening fraction was related to change in transdiaphragmatic pressure in less than 10% of mechanically ventilated patients, our results suggest that one should not use this ultrasound index as a surrogate of diaphragm function. One may argue that diaphragm thickening fraction may be used for qualitative comparisons of diaphragm function within a given patient, but the large variability in diaphragm thickening fraction for a given change in transdiaphragmatic pressure hinders this approach. Also, it could be argued that more participants could have presented with significant relationships between diaphragm thickening fraction and diaphragm function if an increased number of breathing cycles had been analyzed. Although this is true, one must keep in mind that the magnitude may better depict the actual relationship between two parameters than the presence or not of a significant relationship. In the current work, the magnitude of the relationships presented was only moderate, especially in mechanically ventilated patients. Our results highlight the fact that diaphragm thickening fraction poorly reflects transdiaphragmatic pressure. Diaphragm thickening fraction has been extensively studied as a potential criterion for predicting weaning outcome in mechanically ventilated patients,[14,16,17] with cutoff diaphragm thickening fraction values ranging from 25 to 36% that have not been prospectively validated so far. Predicting weaning outcome based on diaphragm thickening fraction is beyond the scope of this work, and our results do not reject any conclusion drawn from these previous works. However, the variability of diaphragm thickening fraction for a given change in transdiaphragmatic pressure across patients may partially explain the different cutoff diaphragm thickening fraction obtained in previous work. In addition, we showed that the diaphragm thickening fraction was poorly related to the pressure generated by the diaphragm, although other measures are available to quantify diaphragm activity, such as diaphragm electrical activity. Recent work showed that diaphragm electrical activity was significantly related to diaphragm thickening fraction ($R^2 = 0.62$).[51] Diaphragm thickening fraction may be more related to diaphragm electrical activity than the pressure it generates, although within-individual analyses are yet to be performed. We strongly encourage future studies to thoroughly describe respiratory cycle selection and analysis to provide readers with an exhaustive and reproducible method. We believe this may, at least partially, improve the comparison of diaphragm thickening fraction–related results across studies. Combining diaphragm thickening fraction with other ultrasound-based techniques such as shear wave elastography,[23,24] speckle tracking,[22,46] tissue doppler imaging,[52,53] or ultrafast ultrasound imaging,[54] may contribute to improving the noninvasive monitoring of the diaphragm function.

Conclusions

Overall, diaphragm function as assessed with transdiaphragmatic pressure was weakly related to diaphragm thickening fraction. The diaphragm thickening fraction should not be used in healthy subjects or ventilated patients when changes in diaphragm function are evaluated.

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Competing Interests

Dr. Gennisson is a scientific consultant for Supersonic Imagine (Aix-en-Provence, France). Dr. Dres received personal fees from Lungpacer Medical Inc. (Vancouver, British Columbia, Canada). Dr. Demoule reports grants, personal fees, and nonfinancial support from Philips (Amsterdam, The Netherlands); personal fees from Baxter (Guyancourt, France); personal fees and nonfinancial support from Fisher & Paykel (Auckland, New Zealand); grants from the French Ministry of Health (Paris, France); personal fees from Getinge (Gothenburg, Sweden); grants, personal fees, and nonfinancial support from Respinor (Oslo, Norway); grants, personal fees, and nonfinancial support from Lungpacer (Vancouver, British Columbia, Canada); personal fees from Lowenstein (Massy, France); and personal fees from Gilead (Foster City, California), outside the submitted work. The other authors declare no competing interests.

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